ADDRESSES AND ORIGINAL ARTICLES

REFLECTIONS ON THE HEALTH CAMPAIGN

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THE fact that the Health Campaign is being …ned by the Prime Minister who has devoted so …ch of his political life to the cause of Health and …at he has by his side our dynamic Minister … Kingsley Wood gives promise of a successful …guration of a considerable venture

Success as distinct from mere publicity value will …pend upon the compass and direction of the cam…ign. Had the Ministry taken counsel with the …dical *profession while the campaign was being* …nned, its programme might have been shaped …ferently; for it has to be remembered that a …alth campaign is a larger and more complex under…king than, say a campaign to extend the benefits … the postal and telephone services, or a campaign … improve recruiting The work of the Ministry of …alth is so voluminous and varied that the compass … the campaign will need to be defined and directed … as to prevent public interest from being dissipated …r in these days when public attention easily tires …ould the campaign outstay its welcome

I suggest that subjects on which the Ministry and …e medical profession have *not worked out a clear* …d settled policy should be excluded from the cam…aign because light and leading would not be forth…oming I will take as an example hospital services …ancy two systems of hospitals in a town—voluntary …d municipal—without any coördinating authority … secure a pattern of services and the financial and …her conditions under which those services are …ailable It is true that a report on this subject …s been in existence since 1920,[1] but no effort has …een made to implement its recommendations or …place the latter by better ones Nor can the useful…ess of the communal services be extended, unless …d until responsible coöperation between the doctors … a district and the medical officers in the service … the local authority has been organised.

Again, what is to be the tune of the propaganda … connexion with the campaign? There is a fear …at when laymen commend the greater use of health …rvices, citizens will gain the impression that they …ave only to sit still and receive benefits— Shut …our eyes and open your mouth, and see what a …rprise! After all, it is only natural that legis…tors should put the weight of emphasis on environ…ental measures which they devise and certainly …eirs is the more popular gospel On the other hand …e doctor *knows that in the last resort health depends* … the individual man—his knowledge still more his …spect for knowledge and his will to live healthily …nd save himself The average doctor would put more …liance on quiet education in smaller communities, …nd would be rather shy of mass meetings preceded …y a pa[illegible] of posters which might give the impres…ion that the Ministry was extolling its own doings …nd affording hopes of rare and refreshing fruit … the future

A HEALTHY RACE

It has been indicated that constructive measures … secure the rearing of a healthy race from before birth to full growth will be in the forefront of the campaign May I express the hope that these measures will be the beginning and end of the campaign to the *exclusion of all other services?* *To-day it is of* national importance to plan for a fit race In former days Nature by her harsh methods went far to secure the strong and sturdy by the struggle for existence and survival of the fittest in short by high death rates which eliminated the weaklings To-day the weaklings are preserved in large numbers are supported partly or wholly by the community marry and produce bad strains and do damage to the next generation Our policy must secure the rearing of fit children, and replace Nature's method of killing the weaklings by a constructive selection of the fittest in body or mind and enabling them to occupy the front ranks of their generation The best of these would become the leaders of their day and in their turn produce a high grade progeny

These ends are likely to be secured by such measures as :—

(1) The provision and availability of good midwifery

(2) The instruction and care of those who wish or expect to become mothers.

(3) Infant welfare clinics

(4) The study and application of the laws of nutrition

(5) Coördinated education of the body and of the mind the teachers of both coöperating with the school doctor

(6) The *provision of the many and various means of* physical recreation and especially for urban populations

I will pass further to consider these measures

(1) *Good midwifery*—It would seem that the comprehensive measures recently passed by Parliament under the guidance of Sir Kingsley Wood are likely to meet this need.

(2) and (3) *Motherhood clinics*—I would urge that the prenatal and infant welfare clinics should become part of a more comprehensive service which I would style 'motherhood clinics' Such a service would embrace those who are contemplating marriage those who are contemplating motherhood expectant mothers and their infants—in short the complete maternal cycle Is there any calling in life for which there is less education than for that of marriage? Knowledge is strength It is needed for the understanding of the claims and implications of sex, for the undertaking of the natural process of pregnancy and without undue and avoidable delay Access to such a clinic would prevent those disharmonies which in cases innumerable create a sense of failure and would often preserve the perplexed from that slippery slope of discontents distempers of body and mind with the dangers of frustrated marriage and an ill nurtured family *It is true that* such a clinic would have to include advice on contraception And why not? It is now an accepted principle that parenthood should result from choice and not from chance and the choice of the occasions for parenthood carries with it the necessity for contraception On the other hand married people often need and welcome advice as to the desirability of adequate parenthood alike in the interests of themselves and their families Is it not time to hope that the Ministry will henceforth recognise that deliberate spacing of children is an accepted practice and in this and other such questions be guided by realities and not by political *considerations?*

(4) The growth of the science of *nutrition* unfolds the prospect of a raised standard of physical and

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[1] Ministry of Health Interim report on the Future Pro… …f Medical and A… …ervices. H.M. Stationery Office. …20 See *Lancet* 1… …, 1823.

gular soldiers. It is true that most large towns ve some sort of aural service but I do not believe ere is a single municipality in the country which s reached full efficiency and I am satisfied that many districts the most appalling neglect persists blic health officials are still hypnotised by the oblems of the school-child to the exclusion of hers It should be realised however that otorrhœa widespread in pre-school infants Many of these ses escape attention others reach the general actitioner or the toddlers clinic The difficulties treating a nervous school-child are enormously creased in a screaming infant. Consequently less pious hopes and carbolic drops are followed a spontaneous cure little more is done

Every case of acute otitis media lasting more than ro or at most three weeks should be automatically dmitted to hospital. It is the experience of every ologist that the bulk of such cases under efficient nservative treatment can be cured within a few ys Of the remainder a few may be lucky enough to velop the classical signs of suppurative mastoiditis nd are submitted to a mastoidotomy that usually res them The residue are only too likely to evelop a chronic otorrhœa These unfortunates art their school life with an established otorrhœa years standing—candidates for the schools for he deaf

CASE 2.—A boy aged 2½ had been ill in a hospital with neumonia during which he developed bilateral otorrhœa n recovering from the pneumonia he was sent to a con alescent home On his return home as the ears were still ouring pus he was brought to my out patient clinic by is mother I admitted him for routine treatment hich failed. He was thereupon subjected to a double astoidotomy and was discharged from hospital a onth later with two dry ears

n this instance the child s hearing has been preserved hanks to the acumen of his mother Far more often owever the otorrhœa is ignored by harassed parents ith the inevitable result

METHOD OF TREATMENT

It may not be out of place here to outline the methods I advocate

Acute otitis—To begin with trained workers are essential. Few nurses indeed few doctors and certainly no parents are capable of cleaning an inflamed ear Nevertheless anyone can be shown in a few lessons how to undertake the treatment. Constant practice alone will ensure the necessary dexterity All my workers have the following printed instructions constantly before them

HOW TO TREAT A RUNNING EAR

Asepsis	Antisepsis
Sterilise your hands Sterilise your instruments Use a sterile towel Use a fresh sterile piece of wool	For each patient.
Use a proper aural forceps.	
Use a good quality (long staple) wool	

Keep the external auditory canal as dry as possible—This may necessitate swabbing away discharge as often as every four hours.

Protect the pinna from irritating discharge—Smear it lightly with a mild mercurial ointment

TO MOP AN EAR OUT

First swab all the pinna with spirit Then tease out a long narrow pledget of wool There must be no loose bits which might get lost in the depths of the meatus.

Never force a fat swab down the ear—It will act like the piston of a syringe and drive pus back into the tympanum and possibly even into the mastoid

If you use a narrow pledget the pus will exude out past it as you push it in

Remember the auditory canal is not a straight tube.—Consequently your straight forceps will not go into it but will bump against the anterior wall To avoid this, pull the pinna as you have been shown No description will make this clear! You must learn by practice

Never push the forceps too far into the canal you may damage the drum.—By altering your grip of the wool you can push it ahead of the forceps right down to the drum without the risk of damage

After using a few dry pledgets use a few soaked in spirit This (*a*) washes away residual pus (*b*) sterilises the meatus; (*c*) shrinks the swollen drum and promotes drainage

Finally dry out the ear again and instil a few drops of the mercurochrome solution Put a large blob of wool loosely into the concha Never pack it in so firmly that discharge cannot get out and never use a small blob of wool which might slip down the meatus unnoticed

The use of spirit sounds barbarous *nevertheless* it is usually quite well tolerated

No more elaborate methods than these are necessary to cure the vast majority of cases within three weeks Occasionally debilitated children will take a week or two longer The otologist must use his judgment here and in general will be prepared to operate *Zinc ionisation which is so valuable in chronic otitis media is absolutely contra-indicated in the acute and subacute stages* It will infallibly precipitate mastoid suppuration.

Chronic otitis media.—We may be dealing here with osseous disease so intractable that even the most radical surgery cannot achieve a dry cavity On the other hand, really conscientious and persistent conservative treatment as in Case 1 will be rewarded in some 70 per cent. of cases by a cure Simple zinc ionisation is our standby Even as used en masse in the minor ailment clinics it has proved itself far superior to all other methods Naturally however the best results can only be achieved by individual study of cases Wherever this clinic treatment fails the child is admitted to hospital for a continuation of his routine treatment Even the dreaded aural polyp can be tackled with considerable hope of cure It may be necessary to snare off the main mass then attack the base with bipolar electrolysis, and only at a later stage to finish off with the usual monopolar zinc electrolysis During the past year I have treated in private six such cases with complete success. By that I mean a cure of the discharge although in most cases there is in addition, a considerable improvement in hearing In one recent case a polyp of some forty years standing had produced a pronounced enlargement of the external auditory canal from simple pressure The ear was stone deaf. Treatment as outlined above finally resulted in a dry ear and a quite useful degree of hearing

RECURRENT INFLAMMATIONS

Let us now consider a type of deafness of which much less is known I refer to that which is due to recurrent catarrhal otitis media Pain being minimal, and discharge absent, the condition is liable to escape notice until parents or teacher realise the child is deaf (or more often suspect it of stupidity) Predisposing causes are very important, amounting to a catarrhal diathesis Unhealthy surroundings inadequate diet faulty hygiene endocrine imbalance produce a child of definite facies and general type A vicious circle is set up as follows

1 Repeated "colds" lead eventually to infection of the paranasal sinuses (mainly the antrum) The latter naturally produces an apparently constant cold with nasal obstruction due to boggy turbinals and mucosa.

2 Hypertrophy of tonsils and adenoids (and allied lymphoid tissue in Eustachian tube), aggravating the mouth breathing

3 Repeated inflammations ensue—possibly sometimes a true tonsillitis or suppurative otitis media, but in many cases a mild but generalised infection of the whole mucous lining of the nose, throat, and ears The child is fretful, has a mild sore throat, and goes deaf I believe many cases of adult "progressive middle-ear deafness" are a late result of these infantile infections

Such a child examined superficially in the hurried atmosphere of a school clinic is found to be a mouth breather subject to sore throats The catastrophic mistake is made of removing the tonsils and adenoids It is not without significance that if the aurist decides to perform this stupid operation under ægis of the municipal authorities he will be paid half a guinea or more If however he removes the child to hospital for a really scientific investigation of the sinuses or other possibilities he will be penalised by having his fee cancelled Consequently with comparatively few exceptions surgery of the nose and throat in school children is limited to the removal of tonsils and adenoids Despite the fact that sinus disease is widespread (Crooks and Signy 1936) and is a potent cause of mouth breathing sore throats, deafness, intractable cough, and general ill health, its very existence is ignored The toll of deafness and ill health mounts daily to the merry click of the guillotine I do not deny that removal of tonsils and adenoids can be a very valuable procedure, but I do say that in cases such as these it is as unsound a procedure as to amputate a blacksmith's forearm in order to deal with the hypertrophy of his biceps The position is truly desperate when catarrhal deafness supervenes Nothing but the most careful attention to all the factors I have mentioned can save the child

PUBLIC HEALTH MEASURES

It is obvious that efficient legislation by public health authorities together with the enthusiastic coöperation of practitioners and otologists could easily make the benefits of this system available throughout the country

I have suggested before that acute otitis media should be notifiable Once a child has been so notified he should be under constant supervision until a competent otologist has certified him as cured Even as there are trained nurses for *ophthalmia neonatorum*, so also should there be trained nurses for otitis media, able to treat and visit sick children in their own homes Any cases that resist treatment for more than two or three weeks must be *automatically* transferred to hospital under a competent and conscientious otologist, no child leaving hospital till his ears are cured To all this must be added a periodic re examination of these children for recurrence of otorrhœa and for diminution of auditory acuity, they must also be excluded from swimming baths

Any such scheme as this must legislate for the child from the day he is born It is folly to restrict aural clinics and such-like activities to the "school child" Very few cases would escape such a system A little education of parents would ensure that they brought up their children as soon as the ear began to run The cost of the system need not be great—certainly no greater than the cost of trying to turn hordes of deafened children into useful citizens The saving of human misery would be incalculable

CONCLUSION

It has become quite a fashion to ascribe our failures in dealing with many diseases to ignorance and delay on the part of the patient Cancer, tubercle, hyperpiesia, &c, all will be cured if only the patient will report at once But in the case of infantile deafness this excuse is specious

The achievements of preventive medicine are the crowning glory of our profession Here ready to our hands is the opportunity for a magnificent piece of work Let us not shelve the blame for its neglect on to the shoulders of our patients It is true that all preventive medicine costs money Legislators responsible for public expenditure cannot be expected to embark on extra outlay unless it is well justified, and consequently the reproach of this horrible affliction will be with us until we bestir ourselves—otologist, practitioner, and medical officer of health—to press more and more urgently for the reforms which I have outlined

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GOLD TREATMENT OF ARTHRITIS

A REVIEW OF 900 CASES

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This paper embodies the results of chrysotherapy in 900 cases of arthritis seen in the Arthritis Clinic of the Leeds Public Dispensary and Hospital, or in private practice during the past four years The results of treatment in the first 100 patients were recorded at the end of the first year (Hartfall and Garland 1935), and the first 400 at the end of the second (1936), these are included in the present review As before, we have adopted the classification of arthritis recommended by the British Medical Association Committee (1933), except that no attempt has been made to subdivide rheumatoid arthritis into "primary" and "secondary" types In applying this classification we have been guided chiefly by clinical observation, but the blood sedimentation rate and radiograms have been used in addition, in a small number of cases the type of arthritis was uncertain, and these are recorded as "unclassified" although it is probable that many of them were atypical cases of rheumatoid arthritis The numbers in the various groups are shown in Table I

The paper is divided into three parts (*a*) Clinical analysis and results of gold treatment in 750 cases of rheumatoid arthritis (*b*) Clinical analysis and results in 150 cases of other forms of arthritis (*c*) Toxic reactions in the 900 cases

It should be noted at the outset that some tables in this paper refer to *cases*, whereas others refer to single *courses* of gold treatment, we have attempted to make this point as clear as possible in the different tables. A large number of figures has been subjected to statistical analysis, although mathematical details have been omitted.

TABLE I

Classification of Cases

Disease	Cases
Rheumatoid arthritis	750
Osteo-arthritis	68
Chronic villous arthritis (climacteric)	23
Spondylitis ankylopoietica	18
Gonococcal arthritis	6
Peri articular fibrositis	17
Unclassified arthritis	18
Total	900

Rheumatoid Arthritis

CLINICAL ANALYSIS

Age and sex.—Of the 750 cases of rheumatoid arthritis 166 were males and 584 females, a ratio of approximately 1 : 4. Table II shows the cases in the different age groups at onset of arthritis and at the commencement of gold treatment. It includes 48 patients who gave a history of previous arthritis, usually of an acute type; in these the age given is that at which the present attack commenced. It will be seen that in a large number of patients the disease commenced in the age-group 40–60. The age-incidence, both as regards onset of symptoms and the commencement of gold treatment, was approximately the same in females and in males.

TABLE II

Age-distribution

Age-group	Cases in age-group: at onset of arthritis	Cases in age-group: at start of treatment
0– 9	5	1
10–19	30	7
20–29	101	40
30–39	160	101
40–49	205	187
50–59	180	242
60–69	63	141
70 +	6	2
Total	750	750

Duration of the disease varied from 1 month to 52 years. In 87 cases it was less than 6 months, in 75 from 6 months to 1 year, in 100 from 1–2 years, in 156 from 2–5 years, in 174 from 5–10 years, in 123 from 10–20 years, and in 37 it had existed for over 20 years.

Onset and progression.—In 458 cases the onset was insidious, in 250 it was acute, and in 42 subacute. The disease had been gradually progressive in 614, in 93 the progression was rapid, and in 43 the course had been characterised by exacerbations and remissions. In 171 patients there was a history of constitutional upset, either throughout or at the onset of the disease—e.g., loss of weight, debility, anæmia, &c.

Disability.—In order to assess the severity of the disease in a simple form we have attempted to grade the disability. While the grouping is quite arbitrary and takes no cognisance of the causes of the disability—i.e., as to whether it was due to pain or joint swelling, muscle spasm, or actual contractures—yet it gives an easy method not only of grading the severity of the cases but of assessing their improvement. Our criteria for the various grades and the distribution of cases are shown in Table III. It may be objected that the criteria laid down for the first two groups are based on a factor (ability to do full time work) which must differ greatly from individual to individual; we have attempted to take such variations into account by altering our standard somewhat in the case of those whose work involves great physical strain. We have not been able to grade all our cases in this way, but those in the Table are representative of the whole group. Although many cases fall into Grade 2, there is a considerable number whose disability is severe.

Family history.—In 127 cases (16.9 per cent.) there were blood relations who had rheumatoid arthritis. This figure is lower than that found recently in America (Dawson and Tyson 1936), but it is greater than in a random sampling of the population. The number of unaffected blood relations is not known.

Association with tuberculosis.—In 15 patients there was a previous history of tuberculosis in the form of adenitis, pleurisy with effusion, or tuberculous disease of bone; in 81 further patients there was a history of tuberculosis in blood relations, and in 62 of these there had been actual contact. In 8 additional cases there had been contact with the disease. There is therefore an association with tuberculosis in 104 cases (13.9 per cent.), probably an insignificant figure.

TABLE III

Distribution of Disability in 534 Cases

Grade	Disability	Cases.
1	Slight disability, but able to do full time work	73
2	Moderate disability, with ability to walk and use the arms, but unable to do full time work.	185
3	Ability to get about, but marked disability of the arms, causing considerable limitation of common activities such as washing and feeding	69
4	Marked disability in the legs—e.g., inability to get up and down stairs—but moderate disability of the arms.	61
5	Marked disability of both arms and legs	39
6	Severe disability in both arms and legs, with inability to walk and more severe disability of the arms than in grades 3 and 5	106
	Very severe disability, the patient being completely bedridden	1
Total		534

Previous treatment.—302 patients (40 per cent.) had undergone some or all of the conventional forms of treatment with little or no benefit in the great majority; 206 cases had had spa treatment, 163 had submitted to other forms of physiotherapy, and 79 had had vaccines (Warren Crowe, stock or autogenous).

Blood sedimentation rate (B.S.R.).—We shall not discuss the B.S.R. in any detail in this paper; its variation in rheumatoid arthritis during treatment with gold is very complex, and we intend to deal with it in a future communication. Briefly, we agree with Forestier (1934) and others that the B.S.R. is usually raised, sometimes very considerably, in rheumatoid arthritis, and as a result of gold treatment a fall usually accompanies clinical improvement. Forestier holds the view that a persistently raised B.S.R. is always an indication for further gold treatment, which agrees with our experience. We have, however, found an occasional rise in B.S.R. in spite of clinical improvement, and although the test is a valuable therapeutic index it is by no means infallible.

Associated conditions were as follows:

	Cases.			Cases	
Hypochromic anæmia— Hæmoglobin (Haldane)			Hypertension— Systolic pressure:		
75–85%	16	46	Over 220 mm. Hg	9	104
65–75%	21		160	75	
Under 65%	9		Raynaud's disease	1	
Addisonian anæmia (1 subacute combined)	5		Albuminuria	3	
Psoriasis	10		Myxœdema	2	
Mitral stenosis	6		Diabetes	[illegible]	
Aortic stenosis	1		Bazin's disease	1	

In view of the fact that more than half of the patients were over the age of 40 it is perhaps not surprising that the incidence of hypertension was high. We have omitted to mention a number of miscellaneous conditions found in this series of cases, as they appear to be of no significance.

METHOD OF TREATMENT

Our experience is limited to Crisalbine (May and Baker) and Lopion (Bayer), given intravenously, and to Myocrisin (May and Baker) and Solganal B oleosum (Schering), given *intramuscularly* In our experience there is nothing to choose between the two routes as regards results or toxic reactions, although intra muscular injection is often easier in the more crippled cases

The injections are given at weekly intervals In our first 100 cases single doses of 0 2 g were given and the total amount of gold salt in one course was approximately 2 0 g, but for the past three years we have not given more than 1 0 g in a course In the past our initial dose was always 0 05 g but recently we have reduced this to 0 025 g The first injection may be followed by an increase of pain, and in that case the initial dose is repeated In the absence of pain *the second dose is 0 05 g and if this* is not followed by pain the third and subsequent doses are 0 1 g until a total of about 1 0 g has been given

A course therefore consists of about twelve injections The interval between courses is at least twelve weeks, and if no toxic symptoms arise in this period a second similar course is always given Similar courses are given at three monthly intervals in any case which *does not* justify the term "cure" or any case of apparent cure with a persistently raised B S R, further treatment is also given in the event of relapse If toxic reactions arise treatment is suspended for a period depending on their type and severity, this is usually about two months after the reaction has disappeared although, as will be discussed later, certain toxic symptoms are a contra-indication to further treatment The above methods of treatment are applied to all forms of arthritis

RESULTS OF TREATMENT

The fact must be emphasised that gold has been the sole therapeutic agent used in the treatment of all cases We have been unable to eliminate the psychological effects of injection therapy, but most observers will no doubt agree that psychogenic factors do not play an important rôle in the majority of patients

Of the 750 patients with rheumatoid arthritis who have been treated with gold during the past four years, 690 had completed one full course at least in April, 1937 Of the remaining 60, 20 had ceased treatment (usually of their own accord) on account of toxic reactions, and 40 had defaulted for reasons unknown

We have previously pointed out the difficulties associated with the tabulation of results in arthritis (1935) and the classification has been slightly modified in the present paper We again use the term "cure" for those patients in whom there is complete relief from pain and disability other than that due to ankylosis, and in whom the blood sedimentation rate is normal Results falling short of this standard, no matter how dramatic, are again recorded as "marked improvement" but between this group and that showing "slight improvement" we are including an intermediate class of "moderate improvement" (These cases fell into the "slight improvement" group in our previous papers)

Table IV shows the results in 690 patients who have completed one course of gold and includes all those seen in the past four years, many of whom have previously been recorded (1935, 1936) Owing to the very large area from which the patients are drawn we have found impossible to keep in touch with every case but 90 per cent of the patients have been seen [illegible] past three months, the remaining 10 per cent are untraceable, and we can only state the results when they were last seen, in many of these this was as much as a year after the last injection

TABLE IV—*Results*

Result.	Cases and percentage		
Apparent cure	68	(9 9)	85 9
Marked improvement	392	(56 8)	
Moderate	90	(13·0)	
Slight	43	(6 2)	
No	61	(8 9)	
Worse	17	(2 5)	
Died (various causes)	19	(2 7)	
Total	690	(100 0)	
Defaulted	60		
Total	*750*		

It will be seen that the high proportion of good results previously observed has been maintained in the present series of cases, almost 86 per cent having shown improvement As is pointed out later, the 19 deaths include 9 cases at least of death from natural causes, and most of these had shown marked improvement before death

Owing to the possibility that cases may relapse, it is of interest to record (Table V) the results in 1937 of the 300 cases recorded in June, 1936

TABLE V

Comparison of Results after Further Observation

	1936	*1937*
Cured	25	35
Marked improvement	208	154
Slight "	45	37
No "	17	23
Worse	1	7
Died	4	10
Untraced	—	34
Total	300	300

While it will be noted that the number of cases showing marked improvement has fallen to some extent, this is to be explained partly by the fact that 11 3 per cent of *the cases have not been traced On the other hand* the cases of apparent cure have risen from 25 to 35 It will also be seen that the deaths have increased by 6, in 2 of these death was due to cerebral hæmorrhage, in 1 it was due to diabetes, and in 3 the cause has not been ascertained These three latter died approximately two years after the last gold injection, and it is almost certain that the cause of death was not connected with gold treatment

The results in relation to the different drugs used are shown in Table VI, this refers to patients who have received one or more complete courses The term "mixed" is used to refer to those who have had *complete courses of two or more different preparations*, this has frequently been due to difficulties encountered in giving intravenous injections As we have already pointed out, larger doses of crisalbine were given at the beginning of this investigation than are given now, and we have classified separately patients who have had more than 1 1 g of the gold salt in any one course Thus "crisalbine A" refers to those patients who have had courses of 1 1 g or less of that preparation, whereas "crisalbine B" applies to cases having had more than 1 1 g in any one course Similarly mixed A and mixed B refer to cases which have had less than 1 1 g and more than 1 1 g of crisalbine respectively in any one course The number of cases which have had more than 1 1 g of preparations other than crisalbine is negligible and it was not thought necessary to consider them separately

TABLE VI

Results in Relation to Different Gold Salts (Patients)

Drug		Cured	Marked Imp	Moderate Imp	Slight Imp	No Imp	Worse	Died	Total	
		No and %	No and %	No, and %	No and %	No, and %	No and %	No and %		
Lopion		41 (10 8)	214 (56 5)	49 (12·0)	27 (7 1)	31 (8·2)	8 (2 1)	9 (2·4)	370	
Solganal		4 (4)	57 (59·4)	14 (14·6)	6 (6 3)	10 (10·4)	3 (3 1)	2 (*)	96	
Myocrisin		0	15 (60)	5 (20)	1 (4)	2 (8)	0	2 (8)	25	
Crisalbine	A	8 (23 5)	13 (38 2)	3 (8 8)	3 (8 8)	4 (11 8)	0	3 (8 8)	34	74
	B	9 (22·5)	18 (45)	4 (10)	2 (5)	3 (7 5)	2 (5)	2 (5)	40	
Mixed	A	1 (1 4)	42 (58 3)	13 (18 1)	4 (5 5)	9 (12 5)	3 (4·2)	0	7	116
	B	5 (11 4)	33 (75)	2 (1 5)	0	2 (4 5)	1 (2 3)	1 (2 3)	44	
Total		68 (9 9)	392 (56 8)	90 (13·0)	43 (6)	61 (8 9)	17 (2 5)	19 (2·7)	690	

Imp = Improvement

It will be seen that the results are better in the crisalbine B and mixed B classes than in the crisalbine A and mixed A classes and statistical analysis shows the difference to be significant. There is evidence from these figures therefore that the larger doses give better results than the smaller ones

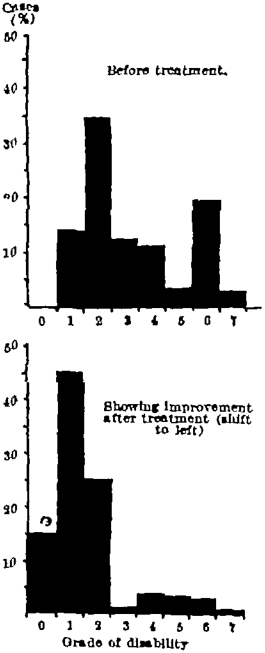
The results for the different drugs have also been subjected to statistical analysis, and it has been shown that the higher number of "cured" cases in the crisalbine A and B classes is significant The interpretation of this however is doubtful as the transference of 8 of the "cured" cases into the "marked improvement" class would make the percentages practically the same for all drugs Thus it would appear from our figures that although the chances of improvement are practically the same with all drugs there may be a greater likelihood of cure with crisalbine than with other preparations

TABLE VII

Relation of Results to Number of Courses

Courses	Cases	Cured	Marked Imp.	Moderate Imp	Slight Imp	No Imp	Worse	Died
		No, and %	No and %	No, and %.	No, and %	No, and %	No and %	No, and %
1	343	45 (13·2)	157 (45·9)	50 (14·6)	25 (7 3)	3 (10 8)	11 (3 2)	17 (5)
2	253	19 (7 5)	162 (64)	31 (12 3)	17 (6 7)	18 (7 1)	5 (2)	1 (0 4)
3	70	3 (4 3)	56 (80)	8 (11·4)	1 (1 4)	—	1 (1 5)	1 (1·4)
4	24	1 (4 2)	16 (66 7)	1 (4 1)	—	6 (25)	—	—
5	1	—	1 (100)	—	—	—	—	—
Total	690	68	392	90	43	61	17	19

In an attempt to discover the factors that influence results of treatment full statistical analysis has been carried out on the inter relationships between duration of disease disability and results of treatment in 534 cases where all three facts were available To save space we have not published the detailed tables but the following conclusions appear to be justified (1) As would be expected there is a significant association between duration and disability the disability steadily becoming worse as duration increases (2) Similarly the results of treatment become significantly worse as duration increases (3) The association between disability and result is not so simple The results in Grade 1 disability are relatively poor but there is an improvement until Grade 3 is reached and then a gradual worsening with increasing disability The explanation of this is not quite clear but it might be accounted for by difficulties in the diagnosis of early and mild cases of rheumatoid arthritis.



The Figure is a graphic representation of the alteration in disability as a result of treatment The black columns represent the percentages of cases in the various grades of disability A pronounced shift to the left is seen.

We have previously suggested (1936) that every patient should have at least two courses of treatment and this is borne out by Table VII The first line shows the results in cases which have had only one course of treatment the possible reasons why these patients have not had second courses are three—many had only completed their first course at the time the results were analysed a few had defaulted and others had had severe toxic reactions. It will be seen that there is a considerable increase in the number of cases showing marked improvement following multiple courses of treatment We have made no reference to the stage at which improvement occurs and although this is a very variable feature it usually commences about half way through the first course of treatment At the same time we have frequently seen improvement commencing after the completion of the first course

Relapse—It is not uncommon to see relapse at some stage after the first or subsequent courses of gold treatment The relapse is most commonly seen about 6 weeks after the last injection, and for this reason Forestier recommends an interval of only 6 weeks between courses Owing to the delay in appearance of toxic reactions, in some cases for more than 6 weeks, we have held the view for some time that the interval between courses should not be less than 12 weeks, feeling that the risk of delayed reaction outweighs the danger of relapse Relapse has occurred in 129 of 613 cases which have been seen within the past 3 months, and the frequency with which it occurred and its severity are shown in Tables VIII and IX

TABLE VIII

Frequency of Relapse

IX

Severity of Relapse

Stage	Relapse	No relapse	Total	Slight	Moderate	Severe	Total
After first course only	81 (13 2 %)	532	613	19	46	17	81
After subsequent courses only	41 (12 9 %)	277	318	14	17	10	41
After first and subsequent courses	7 (2 2 %)	311	318	4	3	0	7

It appears that relapse is a common occurrence after the first or subsequent courses, but a second relapse is a rarity

Other Types of Arthritis

Osteo-arthritis—Of 68 cases, 29 were males and 39 females 7 were over 70, 29 between 60–70, 23 between 50–60, and 9 under 50 Duration of symptoms 2 months–40 years (average 6 4 years) Onset acute in 5 cases, insidious in 63, progress slow in all Only one case had any constitutional disturbance, and in that it was slight B S R (average hourly reading) under 5 mm in 21 cases 6–10 mm in 22, 11–20 mm in 20, and over 20 mm in 2 There was previous vaccine or spa and other physiotherapeutic treatment in 27 cases Hypertension moderate in 11 cases severe in 3 In all cases the diagnosis of osteo arthritis was confirmed by X ray examination

Chronic villous arthritis—Of 23 patients, all fell into the age group 40–60 with the exception of 2 aged 61 and 66 Duration of symptoms 3 months–10 years Onset acute or subacute in 6 cases, insidious in 17, progress slow in all B S R (average hourly) under 5 mm in 11 cases, 6–10 mm in 3, and over 10 mm in 7

Spondylitis ankylopoietica—Of the 18 cases, 13 were males and 5 females, aged 22–56 Duration 2–13 years, progress gradual in 18 2 showing acute exacerbations History of some constitutional upset in 11 cases Associated hypochromic anæmia in 6 cases, hæmoglobin 65–78 per cent (Haldane) B S R (average hourly) under 10 mm in 3 cases, 11–20 mm in 7 20–40 mm in 3, and 40–80 mm in 4 Cases of rheumatoid arthritis with spinal involvement are not included in this group

Peri articular fibrositis—Of 17 cases 8 were males and 9 females aged 26–65 Duration 6 months–30 years B S R (average hourly) under 10 mm in 12 cases, 10–20 mm in 2, and 42 mm in 1

Gonococcal arthritis—There were 5 males and 1 female aged 29–42 Duration 6 months–10 years History of gonorrhœa in all 6 Onset of arthritis acute in 4 cases, and gradual in 1 B S R raised in 2 cases

Unclassified arthritis—There were 13 females and 5 males aged 29–75 B S R (average hourly) under 10 mm in 13 cases, and in 2 between 11 and 20 Probably several of these were atypical examples of rheumatoid arthritis

RESULTS

With the exception of the osteo arthritis group, the numbers are much too small to enable us to draw any definite conclusions (Table X) With regard to osteo arthritis some improvement was seen in more than half the cases, but the results were not comparable to those seen in rheumatoid arthritis, and we feel that gold is not likely to play an important part in the treatment of this disease The good results seen in the few cases of "unclassified" arthritis again suggest that some of these may have been atypical examples of rheumatoid arthritis

TABLE X

Results in Other Forms of Arthritis

Disease	Cases	Cured	Marked imp	Moderate imp	Slight imp	No imp	Worse	Died
Osteo arthritis	68	0	10	11	19	22	6	0
Climacteric arthritis	23	0	7	7	5	3	1	0
Spondylitis	18	0	5	2	8	3	0	0
Peri articular fibrositis	17	0	2	2	6	6	1	0
Gonococcal arthritis	6	1	2	0	1	2	0	0
Unclassified arthritis	18	5	6	3	1	2	0	1

(To be concluded)

AN INQUIRY INTO "RELAPSE" FOLLOWING SYMPATHECTOMY

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In previous communications Telford (1932, 1934) reported the disappointing results of cervico thoracic ganglionectomy for the Raynaud phenomenon in the fingers The frequent failure to prevent the attacks was the more surprising because of the permanent success of lumbar ganglionectomy in the treatment of the same condition in the feet This proved to be the experience of all surgeons working in this field of vascular diseases (Gask and Ross 1934, Ross 1935, Livingston 1935, Adson and Brown 1929) and it led directly to a belief, widely held in this country, and in America, that stellate ganglionectomy was in some way incomplete, in that it left intact some of the vasomotor nerves reaching the upper extremity Anatomical variations in the vasomotor pathways to the arm were soon demonstrated (Kuntz 1927, Sheehan 1933) and were followed by modifications of the operation which resulted in the inclusion of the second and third ganglia in the excision

The clinical results, although better, showed that despite complete sympathetic denervating of the arm, there were still relapses with recurrence of the Raynaud phenomenon. Many theories have been advanced to explain this finding and these will be discussed in detail below Suffice it to say here that each theory has failed to explain all the known facts and that therefore none of them is entirely satisfactory at the present moment

In this clinic the realisation that lumbar ganglionectomy is largely a pre ganglionic section of the vasomotor nerves of the foot whereas cervico thoracic ganglionectomy is a post-ganglionic excision for those of the arm led Telford (1935) to modify the technique of the cervical operation by making a pre ganglionic section. This operation section of the sympathetic cord below the third thoracic ganglion together with division of the rami of the second and third thoracic nerves, has been carried out by Telford since 1935. Independently Livingston (1935) and Smithwick (1936) in America performed a similar operation employing however a different method of approach.

Physiological support for such an operation, which is almost entirely a pre ganglionic section for the arm has been brought forward by Freeman and others (1934) and Smithwick and others (1934). They pointed out that smooth muscle when deprived of its nerve-supply became hypersensitive to adrenaline a reaction which had been described earlier by Lewandowsky (1903) and confirmed by Meltzer and Auer (1904), Elliott (1905) and Dale and Richards (1918). White and his co workers (1935 1936 1937) applying this principle to the results of sympathectomy in the vasospastic conditions of the extremities were able to show that pre-ganglionic section of the vasomotor nerves rendered the blood vessels *less* sensitive to adrenaline than did complete denervation by post-ganglionic excision. This has been confirmed in animals by Grant (1935) and by Ascroft (1937).

These latter papers important as they are deal with observations on animals and the findings are not necessarily true for the human subject. The abundant material in Prof. Telford's clinic (260 cord ganglionectomies in all) has afforded us the opportunity to carry out a series of observations on the post-operative conditions of these sympathectomised patients. We had as material for the research a large number of stellate ganglionectomies done between the years 1931–34 and a smaller number of pre ganglionic sections of the thoracic cord done since February 1935. In two patients we had the advantage of an exact control because they have had a post-ganglionic excision on the one side and a pre-ganglionic section done at the same time on the opposite side. Our object has been, by carrying out observations on sweating ulnar nerve block and the intravenous administration of adrenaline to estimate the results and relative value of the post- and pre-ganglionic operations in the human subject. Since the majority of the pre-ganglionic cases are of less than two years duration, it is of course possible though we think it unlikely that lapse of time may cause us to modify our conclusions. The results of this investigation which is still in progress will be published in detail later but certain facts which have already emerged from the study appear to be of sufficient importance to deserve publication.

THE SWEATING MECHANISM

Absence of sweating induced by heat has been generally accepted as evidence of the completeness of sympathetic denervation of a limb for it is undoubtedly true that the sudorific and vasomotor nerves to an extremity follow similar anatomical pathways to the periphery. In this investigation the sweating mechanism has been tested by warming the patients in a cage fitted with electric bulbs, and the presence of sweating has been outlined by the iodine-starch method. It has been possible to demonstrate that reflex sweating of the hands following exposure to the heat of the body only never occurs immediately after a complete sympathectomy whether the post or pre ganglionic operation has been carried out. If however the hands of such patients are placed under the cage and thus subjected to direct heat sweating is invariable. This sweating in response to direct heat will occur over the ulnar side of the hand even after ulnar nerve block at the elbow. It seems important therefore to emphasise that it is only the absence of *reflex* sweating that indicates complete interruption of all vasomotor nerves. With this proviso the method is a certain guide to the completeness of any operation. By this means it has been possible to eliminate one or two cases from the present series patients who showed reflex sweating of the hands immediately after operation. In such cases anatomical difficulties have resulted in section of only part of the sympathetic cord giving an incomplete result.

In true cases of relapse the patient is only gradually aware of the return of perspiration to the hands but this can always be shown to be present by means of a reflex sweating test. Furthermore in these patients, sudorific fibres can be demonstrated in the ulnar nerve since anæsthetisation at the elbow prevents *reflex* sweating in the ulnar area of the hand.

ULNAR NERVE BLOCK

Injection of the ulnar nerve at the elbow with 2 per cent. novocain has been carried out both before and after operation. A reddening followed by a rise of temperature over the ulnar side of the hand, indicates the unquestionable existence of vasoconstrictor fibres in the ulnar nerve. The absence of these colour and temperature changes in the presence of *complete* ulnar nerve anæsthesia and palsy is not so decisive in ruling out all vasoconstrictor fibres to the ulnar area of skin. Lewis (1929) failed to obtain any such rise in skin temperature in several cases of severe Raynaud's disease (unoperated) in which he had blocked the ulnar nerve at the elbow. He interpreted his findings as a proof of the existence of a local fault in the digital vessels, these remaining in spasm despite the removal of all vasoconstrictor impulses. The severity of the condition in his patients who showed ulcerative gangrene at the tips of the fingers suggests that there may have existed a local pathological lesion in the digital vessels, which would complicate the picture of simple vasomotor spasm.

Simpson, Brown, and Adson (1931) have however considered the possibility of an accessory median supply to account for the persistent vasoconstriction in the fourth and fifth fingers after ulnar nerve injection and in their experiments they infiltrated the bases of these digits in addition. Ascroft (1937) criticises this method on account of the vascular dilatation which follows local injection of novocain. White (1935) supports this view of an accessory median supply for he finds that even in severe cases when ulnar nerve block has failed to raise the skin temperature a subsequent median nerve injection will invariably do so. The ulnar and median areas in the palm of the hand and fingers unquestionably overlap, and there are considerable connexions between the two nerves. The nerve-supply to the palmar arches may be derived from both sources, but as the median nerve has never been known to supply any sensory branches to the fifth finger it is highly improbable that it innervates the digital vessels of this finger.

The value of the test has been discussed in some detail because of criticisms that have been made against it as a reliable method of investigation. Briefly it can be stated that there can be no dispute as to the meaning of a positive finding—i e, an immediate rise in skin temperature over the fifth finger, following ulnar nerve block at the elbow It indicates clearly the presence of vasoconstrictor fibres in the ulnar nerve In this investigation it is this positive finding which has been of the greatest value A negative result is, for reasons stated above, open to question, but in order to put this point to the test more critically the experiment has been carried out before and after operation on the *same* patients, under exactly similar conditions, and with the same room temperature Before operation, ulnar nerve injection has invariably resulted in an immediate rise of the skin temperature of the fifth finger and ulnar side of the hand within 15 minutes, without any accompanying rise in the first, second, and third digits In the same patient, immediately following complete sympathectomy, whether post or pre ganglionic, no rise in skin temperature has ever occurred These negative findings are conclusive evidence that the operation has divided all vaso constrictor fibres which pass along the ulnar nerve

We have demonstrated that in every patient who has shown signs of clinical relapse after sympathectomy, whether post or pre ganglionic, a rise in skin temperature of the little finger has followed ulnar nerve block at the elbow Two cases, who have regularly attended for testing since their operation, eventually showed a rise in skin temperature, followed later by a clinical relapse The remaining cases, which have shown no clinical relapse after operation, have never revealed any rise in skin temperature, although the test has often been repeated in the same patient

INTRAVENOUS ADRENALINE

The test carried out is that devised by Freeman, Smithwick, and White (1934)

Normal saline is run into the median basilic vein at a slow rate, 40–60 drops per minute After a period of half an hour the saline is stopped and an adrenaline solution of 1 in 250,000 strength substituted without the patient being aware of the change The adrenaline solution is run into the vein at the same rate for a period of a half to one hour, and skin temperature and pulse readings are taken at five minute intervals

The procedure is accompanied by no pain apart from the initial insertion of the needle, and except for slight headache and some palpitation no unpleasant symptoms are experienced There is always striking pallor of the face, especially in the circumoral region, and of the hands and fingers, which appears 5–10 minutes after the adrenaline has been started, and which persists until 3–4 minutes after the adrenaline has been stopped In the fingers and hands the pallor is followed by a fall in skin temperature, if this temperature is above that of the room The pallor of the face, and in particular of the circumoral region, is not accompanied by any appreciable drop in skin temperature, indicating that here the effect is mainly on the minute vessels Broadly speaking, the higher the initial skin temperature of the hand, the greater the fall in temperature When the adrenaline is stopped, there is a profuse blushing of the face within 3–4 minutes, followed in 5–10 minutes by a similar flushing of the hands With the reddening of the hands there is a rapid rise in skin temperature, up to that of full vasodilatation This reaction appears to be similar in many ways to the "over swing" occurring in response to cold, described by Lewis (1930) Where the temperature of the fingers has been initially low—i.e, about room temperature—no further drop can occur, yet when the adrenaline has been stopped a rapid "overswing" up to a high temperature may occur, indicating release from a vasoconstrictor effect of the adrenaline In the later experiments, full vasodilatation has been produced by placing the hands under the bedclothes before commencing the experiment

The observation of Freeman, Smithwick, and White (1934), that following pre ganglionic section the drop in temperature is less than after postganglionic excision, has been confirmed. In two patients, in which a pre ganglionic section has been performed on one side and a post-ganglionic excision on the other, the difference in sensitivity to adrenaline has been watched over a period of 6 months, but after both types of operations this sensitivity has decreased with time The great difference between the reaction to adrenaline following the two operations (post and pre ganglionic) in the monkey (Ascroft 1937) does not appear to be so evident in man Of greater importance is the fact that in those hands which show a clinical relapse after operation, the reaction to adrenaline is considerably less than in those with no relapse

DISCUSSION

The search for the cause of the relapse of the Raynaud phenomenon following sympathectomy for the arm is one of the largest problems to day in vascular surgery Clearly all cases of incomplete operation, as revealed by reflex sweating and no clinical improvement immediately after sympathectomy, must firstly be excluded These cannot be regarded as cases of *relapse* Relapse implies an interval of complete recovery, or at least a considerable degree of relief from the attacks Obviously such relief must be adequately tested by exposure to external temperatures which, before operation, gave rise to spasm This point is not always taken sufficiently into account in judging the immediate results of sympathectomy

Excluding these operative failures, there remains a large group of cases which have shown a definite improvement, or complete absence of attacks for several months after ganglionectomy and have then begun gradually to relapse At first the attacks are only produced by very prolonged exposure to severe cold and they are never as severe as before operation Gradually the attacks of spasm become more frequent and more severe, and are brought on by shorter exposures to milder temperatures Finally after a year or more the patients complain that their hands are "almost as bad as ever," though they frequently volunteer that the fingers now go blue rather than white The time of relapse varied from patient to patient, in some cases it is as early as six months, in others it is not manifest for nine or even fifteen months Relapse is not an invariable sequel and there are patients in the clinic, on whom cervico thoracic ganglionectomy was performed 4½ years ago, who have never had any attacks in the hand since the date of operation In considering any theory of the cause of relapse, we must account for the several months of relief which follow every complete sympathectomy and for its permanence, even in the arm, in occasional cases

Lewis (1929) believes that the explanation is a local fault in the digital vessels, an over-action of the vessel in response to stimuli apart from nervous impulses Unquestionably the vessels of the skin are under the influence of many factors, nervous impulses, hormonal substances and chemical alterations in the blood, and chemical substances liberated in the tissues Any of these acting singly, or in combination, may bring about an excessive reaction, resulting in spasm of the arterioles That the vessels in different parts of the body react differently under the same conditions has been clearly demonstrated by Lewis. In the present investigation we have found that the digital vessels of the hand respond more quickly and more vigorously than the corresponding vessels in the toes Yet it is difficult to believe that Lewis's theory accounts for the relapses following sympathectomy for the arms for it does not explain the complete cure invariably following lumbar sympathectomy and occasionally seen after cervico thoracic ganglionectomy Nor does it account for the period of relief which precedes the relapse in the arm If the local fault remains after the removal of vasoconstrictor impulses reaching the vessels along nervous pathways it is difficult to see why it should manifest itself in some arm cases and not in others

The hypersensitivity of the vessels to adrenaline following sympathectomy which has been demonstrated by White and his colleagues (1936) will account for the drop in skin temperature occurring a few days after operation and becoming permanent. This hypersensitivity however cannot be held responsible for the clinical relapse which is observed after a definite time interval of 6–15 months because the hypersensitivity is revealed 8–10 days after operation. Furthermore from our observations it seems that this reaction of the blood vessels to adrenaline is at its greatest when it first appears and that it tends to decrease being less evident at the time that clinical relapse occurs In addition pre ganglionic section in the arm several times relapsed in this clinic and much sooner than the ganglionectomies

Five or six days after a cervico thoracic ganglionectomy the skin temperature of the hand falls and the hand will be invariably colder than one in which pre ganglionic section has been performed It remains in this condition for at least six months before actual recurrence of the attacks supervenes Surgically it is regarded as an incomplete cure though the patients are usually very satisfied with the result Gradually the attacks reappear and the condition is admitted by both surgeon and patient as one of relapse The typical history of a relapse after pre ganglionic section is rather different The hand remains hot and a good colour with complete absence of all spasm, in every way resembling the feet after lumbar sympathectomy When relapse supervenes it happens quickly and completely and we have had three patients return after an interval of 2–3 months and one after 6 months.

There remains to be considered the possibility of regeneration. Against this view there is the obvious difficulty of visualising regeneration of pre-ganglionic fibres which would function in the absence of post-ganglionic cell stations that is after excision of the inferior cervical and upper three thoracic ganglia Regeneration after simple pre ganglionic section is easier to understand. But this theoretical difficulty is counterbalanced by several factors which if they do not prove at least suggest the possibility of regeneration In the first place the relapses that have followed after pre ganglionic section have all occurred within 6 months after operation, whereas following post ganglionic excision, a true relapse has not been seen before 6–9 months and has been as much as 15 months. The gap left by a pre ganglionic section where no attempt has been made to separate the cut ends is very small, and regeneration if it occurs would be expected sooner than after a wide ganglionectomy For this reason Telford has stitched up the upper cut end of the sympathetic cord to the scalenus muscle in all the recent operations None of these pre ganglionic sections have shown any sign of relapse whereas by contrast four earlier pre ganglionic sections in which the upper cut end was not stitched up have all relapsed

The results of the ulnar nerve injections in this investigation have demonstrated the presence of vasoconstrictor fibres in the ulnar nerve in all patients who have clinically relapsed after sympathectomy whether post or pre-ganglionic In one case a rise in skin temperature of the little finger and ulnar side of the hand has reappeared for the first time 6 months after operation It was not present when the ulnar nerve was blocked 6 weeks and again 3 months after the operation The rapidity of regeneration of sympathetic fibres is well known and regeneration would account for the period of several months of relief preceding the relapse and for the gradual progression of the relapse when it does occur It is not difficult to understand the permanency of some cases of stellate ganglionectomy and the good results of lumbar cord ganglionectomy with its wider excision, when one remembers that regeneration of nerves commonly fails to establish exact anatomical union and still more often shows defects of physiological recovery

It is not meant here to convey that regeneration accounts for all relapses following cervico thoracic sympathectomy The arguments that have been brought forward are by no means conclusive and furthermore they are based on only a few cases The problem is not yet solved and regeneration of vasomotor nerves may be only part of the explanation The facts do suggest, however that before any theory of extrasympathetic vasomotor pathways is advanced to explain the reappearance of vasoconstrictor fibres in the ulnar nerve the possibility of regeneration should and must be excluded

SUMMARY

A series of patients in whom the cervico thoracic ganglion has been removed or its pre-ganglionic fibres divided has been investigated by sweating tests ulnar nerve block and giving dilute adrenaline intravenously

The results do not support the explanations of the cause of relapse after sympathectomy offered by Lewis in England and White in America.

It has been found that the relapse coincides with the reappearance of vasoconstrictor fibres in the ulnar nerve It is suggested that regeneration of sympathetic fibres must explain their reappearance

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THE BACTERIOSTATIC ACTION OF *p*-AMINOBENZENESULPHONAMIDE UPON HÆMOLYTIC STREPTOCOCCI

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THE work of Colebrook, Buttle, and O'Meara (1936) and Fuller (1937) has established that *p* amino benzenesulphonamide, when administered as such or obtained by the cleavage of the more complex substances 4-sulphamido 2 4′ diaminoazobenzene and disodium 4-sulphamido phenyl 2-azo 7 acetylamino 1-hydroxylnaphthalene 3′6′ disulphonate, is bacteriostatic towards hæmolytic streptococci. Colebrook demonstrated its action in blood in vitro by using the slide cell technique and by setting up similar organism blood mixtures, containing sulphanilamide, on Todd's moving machine, determining the fluctuations in bacterial population at intervals Although sterilisation occurred eventually, he noted that in the earlier phases of incubation the cocci multiplied No attempt was made to assess the part played by fixed tissues in dealing with infection by hæmolytic streptococci

In view of the importance of these observations it seemed necessary that this work should be confirmed Investigations have been made also upon any modification of other defence mechanisms that might be caused by sulphanilamide Our inquiry has concerned the part played by (1) the blood, (2) polymorphonuclear leucocytes, and (3) the reticulo endothelial system Attention was also given to the possible toxic effects of sulphanilamide upon these tissues

ACTION OF SULPHANILAMIDE IN BLOOD

Normal defibrinated blood with and without sulphanilamide, and normal defibrinated blood rendered leucocyte free by Fleming's method,[†] have been seeded with hæmolytic streptococci and the fate of the latter determined after incubation, using the slide cell technique The results of many such experiments are substantially the same as those obtained by Colebrook although it is considered that this technique gives qualitative rather than a true quantitative representation of the bactericidal power of blood A typical experiment is shown in Table I

In similar bactericidal experiments performed on Todd's moving machine sterilisation was effected in the blood containing sulphanilamide, whereas growth persisted in the controls Sterilisation of the blood appears to be slow—i e after eight hours' incubation Moreover in all the experiments where the population was assessed by hourly explantation the organisms in the blood containing sulphanilamide passed through a phase—early in incubation—during which multiplication was excessive when compared with the controls When the acme was reached the decline in population was extremely rapid An example of this is given in Table II

TABLE I

—	Cocci in original implant		
Colonies developing after 24 hours incubation of 60 c mm of—	108[*]	575[*]	1900[*]
Normal defibrinated blood	10	41	71
Ditto plus 1/10 000 sulph	0	0	0
Ditto plus 1/20,000	0	0	2
Normal defibrinated and deleucocyted blood	33	87	Inf.[†]
Ditto plus 1/10 000 sulph	0	0	0
Ditto plus 1/20,000	0	0	0

Sulph. = sulphanilamide

[*] Determined by separate explantations into melted blood agar

[†] Complete hæmolysis of content of slide cell with a uniform granular growth.

Cells showing no growth were dismantled after a further 24 hours incubation and the contents proved sterile by explanting into serum broth

TABLE II

Normal defibrinated blood with and without sulphanilamide (concentration 1/15,000) implanted with dilutions of 14 hour culture of hæmolytic streptococci and incubated at 37° C on Todd's moving machine, explants being made at intervals into melted blood agar

Colonies developing from 100 c.mm explanted at—	Cocci implanted per 100 c.mm					
	1250		400		68	
	Contr	Sulph.	Contr	Sulph	Contr	Sulph.
2 hours	558	1400	278	253	15	253
3 "	470	2800	177	338	24	383
4 "	423	5000	103	173	59	179
6 "	361	72	50	10	353	11
8 "	315	35	74	2	702	1
24 "	296	0	24	0	40	0

This sudden fall in population following the rapid rise might be explained in one of three ways —

1 Sulphanilamide may have a much more efficient bactericidal action upon cultures that have passed through the logarithmic phase of growth than upon young cultures

2 Sulphanilamide may be slowly changed into some other compound which is the actual bactericidal agent

3 Sulphanilamide may have a slowly engendered stimulatory action upon the normal mechanism of organismal destruction in the blood

Considering the third postulate, the normal mechanism of destruction in the blood seems necessarily dependant upon primary phagocytosis Colebrook has shown, and his experiments have been confirmed by one of us, that sulphanilamide is able to kill hæmolytic streptococci in blood whether leucocytes are present or not For this reason the third postulate seems improbable and therefore was not tested experimentally at this stage

Age of streptococcal culture and its relationship to bacteriostatic effect of sulphanilamide in blood—A series of cultures, wherein the total volumes and amount of original implant were standard, were made in serum broth and incubated at intervals so that they reached graded ages at the same time The cultures were enumerated by Wright's method,‡ and diluted so that their concentrations were approximately equal From these diluted cultures standard volumes were seeded into blood containing 1/10 000 sulphanilamide and the blood-organism series incubated at 37° C on Todd's moving machine Population curves were constructed by enumerating the number of colonies developing from standard volume explants made at intervals in melted blood agar The results of such an experiment set out in Fig 1 show that young streptococci pullulate very rapidly in the presence of sulphanilamide when the peak of growth is reached the population falls away extremely fast With increasing age of cultures this rise and fall becomes progressively less pronounced and in the 20 hour strain the organisms are almost immediately susceptible to the bactericidal action of sulphanilamide There is thus experimental evidence to support postulate 1

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[*] The expenses of this work were partly defrayed by a grant to one of us from the Medical Research Council

[†] Films of the blood, made after filtering it through cotton wool and spread with an opsonic spreader which drags the leucocytes to the end of the film were examined and no leucocytes were found Evidently the efficacy of Fleming's method depends on the closeness of packing and the amount of cotton wool used. The method was tried out with these two points in view before the test proper was done

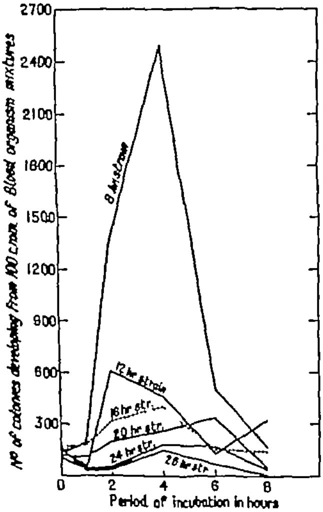

FIG 1.—Relation between age of culture and survival in blood containing 1/10 000 sulphanilamide.

The question as to whether sulphanilamide was converted into another substance was investigated by seeding 10 c.cm quantities of blood and of broth both containing sulphanilamide with 1 c.cm of undiluted culture of streptococci, controls being seeded with 1 c cm of serum broth Estimations of sulphanilamide were made by the diazo reaction method described by Fuller before and at the end of 24 hours incubation No significant reduction in the amount of the drug was detected in any of these tests with the exception of the control bloods We were at first at a loss to explain this apparently anomalous result, but later it was thought that by analogy with results to be recorded below this apparent diminution in the concentration of sulphanilamide in control bloods was due to its slow solution in the lipoid envelopes of the red cells In Fuller's method precipitation of proteins by trichloracetic acid also removes red cells in the tubes containing blood and organisms complete lysis had occurred at the end of 24 hours incubation and it is possible that any sulphanilamide dissolved in the red-cell lipoid might have escaped removal with the protein precipitate

Mode of action of sulphanilamide in producing bacteriostatic effects upon hæmolytic streptococci—It has appeared somewhat surprising that sulphanilamide a compound so relatively simple chemically and so sparingly soluble in aqueous solution should have such a definite bacteriostatic effect upon hæmolytic streptococci. It is well known that its solubility is increased in certain fat solvents such as acetone and the question arose as to whether sulphanilamide is more soluble in fats more especially the fatty substance that can be recovered from acetone and ether washings of washed hæmolytic streptococci

A quantity of this fat was recovered by the method employed by Heidelberger and Kendall (1931) and an emulsion was made in 10 c.cm. of water containing sulphanilamide such that the final concentration of fat was 1/50 and that of sulphanilamide 1/2000 A control containing no fat was also set up Both volumes were incubated in sealed tubes at 37 C for two hours on Todd's moving machine and at the end of this time the fat was removed by prolonged centrifugation and the concentrations of sulphanilamide in the aqueous portion re-estimated No change was found in the control tube but in the tube previously containing streptococcal fat the concentration had fallen to 1/3810

Original weight of sulphanilamide in 10 c.cm	—	0·006 g
Original weight of fat in 10 c.cm	—	0·20 g
Calculated final weight of sulphanilamide in aqueous solution	—	0·0027 g
Calculated final concentration of sulphanilamide in fat	—	1/60

Repetition of this experiment, using variations of the original concentrations of sulphanilamide and of fat did not give a constant partition coefficient but the final calculated concentration of sulphanilamide in fat came to 1/100 in one case and 1/95 in the other There seems little doubt that sulphanilamide is therefore far more soluble in the fatty envelope surrounding hæmolytic streptococci than in aqueous solution and it is highly probable that sulphanilamide owes its bacteriostatic action upon hæmolytic streptococci to the fact that the drug is initially concentrated in the fatty envelope The possibility also presents itself that heterophile bacteriostatic actions such as the recorded actions of sulphanilamide upon meningococci are due to a similar solvent action by organismal fat

From these results two striking features stand out

1 The growth of young streptococci in blood is stimulated by sulphanilamide

2 Sulphanilamide is more soluble in streptococcal fat than in aqueous solution

The question immediately presented itself as to whether these two facts were related Standard volumes of glucose bicarbonate medium made by a method similar to that described by Todd and Hewitt (1932) were seeded with standard volumes of a 14 hour culture of hæmolytic streptococci These were incubated at intervals so that the resulting cultures

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‡ A mixture of blood the red cell count of which is known is made with the bacterial culture and the number of bacteria is compared with the number of red cells (Wright 1912)

In this experiment the streptococcal chains were completely broken up by introducing the culture into a hard glass tube containing about c.cm volume of small glass beads The tube was closed with a rubber bung and the chains of streptococci were disintegrated by holding the tube against a rotating eccentrically mounted rubber bung on the end of a centrifuge spindle reached graded ages at the same time The organisms in each culture were removed by centrifugation, washed twice in saline, and the fat extracted by the method used before The weight of fat and the weight of dried defatted organisms was determined in each case The results given in Fig 2 show that as age of culture increases the percentage of fat diminishes

It is difficult to correlate the presence in young cultures of a higher concentration of fat—a relatively good solvent of sulphanilamide—with the fact that sulphanilamide stimulates the growth of young streptococci Two explanations are possible (1) that with the diminution of the percentage of fat as age increases, the concentration of sulphanilamide in the fat of each individual cell increases, and this increase is responsible for the bacteriostatic action upon older cultures, or (2) that sulphanilamide acts first as a stimulant and secondarily as a depressant, such a pharmacological action is not unknown, and that of nicotine may be instanced as a parallel We have made no attempt to decide which is correct, although the second seems the more probable

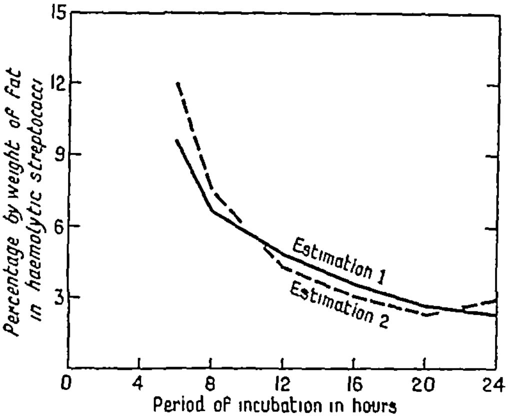

FIG 2 —Relation between age of culture and percentage weight of fat

The stimulatory action of sulphanilamide has been demonstrated not only in vitro but also in experimental infection

Rabbits were given, daily for one month via a stomach tube 0 6 g sulphanilamide in water acidulated with hydrochloric acid Control rabbits were given similar volumes of acidulated water At the end of this time, and two hours before infection, further doses of sulphanilamide were administered Both control and experimental animals were then injected intravenously with 0 2 c cm of a 12 hour culture of hæmolytic streptococci of moderate virulence At intervals 1 c cm of blood was withdrawn from the veins of the rabbits and explanted into melted agar The plates were incubated and colony counts made on the following day One series of animals was killed eight hours after infection, the others being killed on the sixth day In Table III are given the results of such an experiment

The spleens and livers of the animals killed eight hours after the intravenous injection of hæmolytic streptococci were sectioned and by suitable staining (Gram's method) the streptococci which had been ingested by the reticulo endothelial cells were demonstrated

No diminution in the activity of the reticulo-endothelial system was detected in those rabbits that had received sulphanilamide It therefore appears that the difference between the number of organisms present in the circulating blood of the two sets of animals is due to an actual stimulation of growth of organisms within the blood by the action of sulphanilamide This stimulation could only be demonstrated when the administration of the drug was discontinued at the beginning of the stage of experimental infection

EFFECT OF SULPHANILAMIDE ON THE ACTIVITY OF HUMAN POLYMORPHONUCLEAR LEUCOCYTES

The effect of sulphanilamide upon mobility and phagocytosis by polymorphonuclear leucocytes was also investigated Living leucocyte preparations were made by the method described in a previous paper (Paine 1935), and exposed in a 10 per cent serum solution in Tyrode's solution containing 1/1000 sulphanilamide Observations over a period of six hours showed no change in the appearance or motility of leucocytes

Similarly no significant changes were found in their phagocytic activity, although the cells were only exposed for thirty minutes to the action of sulphanilamide A series of tubes containing nine parts of normal defibrinated blood containing sulphanilamide in concentrations varying from 1/1000 to 1/20,000 and one part of a 14 hour culture of hæmolytic streptococci, known to be amenable to phagocytosis, were incubated on Todd's moving machine at 37° C for thirty minutes Controls without sulphanilamide were similarly treated At the end of incubation, opsonic films were examined, the cocci in 200 polymorphonuclear leucocytes being counted on each film

The results showed that neither depression nor stimulation of phagocytic activity had occurred during incubation

Sulphanilamide and bone marrow activity —Sulphanilamide was administered in 1 2 g doses daily via a stomach tube to six rabbits Of these two died in the fourth week All showed a progressive loss of weight, but the four survivors ceased to lose after three weeks The average loss of weight was approximately 500 g Administration of the drug was discontinued after six weeks when the animals were killed During the whole of this period, blood counts were made on alternate days Little change was noted in the red cells, but there was evidence that the drug had a definite action upon the bone marrow, as shown by crises when the total white cell count was greatly increased, on some occasions rising to 30,000 per c mm These high counts were due to polymorphonuclear increments and were associated with showers of abnormal and nucleated red cells the reticulocyte counts remained almost unchanged Interesting in this connexion is the fact that showers of abnormal and

TABLE III

Time after infection	Colonies developing from explant of 1 c cm of blood from—		Time after infection	Colonies developing from explant of 1 c cm of blood from—	
	Exp animals	Control animals		Exp animals	Control animals
30 min	30	110	6 hr	119	6
60 „	1	40	12 „	201	17
90 „	0	122	30 „	451	0
120 „	2	5	48 „	43 750	0
3 hr	6	36	100 „	11	0
4 „	13	4	144 „	0	0
5 „	5	1			

Exp = experimental

nucleated red cells have been seen in the blood of women suffering from puerperal infection whilst under sulphanilamide treatment

In addition to the effects described above cyanosis of the lips and mouths of the rabbits was noticed This persisted as long as twenty four hours after the administration of the drug and was accompanied by dilatation of the pupils Of the two rabbits that died, both showed petechial hæmorrhages in the gastric mucosa and in the muscles and connective tissue One also showed an extensive hæmorrhage into the psoas muscle Gastric mucosal hæmorrhages were also found in the other rabbits

SULPHANILAMIDE AND THE RETICULO-ENDOTHELIAL SYSTEM

The effect of sulphanilamide on the reticulo endothelial system was studied by determining whether ingestion and absorption of the drug caused any alteration in the phagocytic activity of the reticulo endothelial cells of the spleen

The technical method adopted was to outline the phagocytic cells of the spleen by the intravenous injection of india ink. Each of six rabbits was given 1 5 c cm india ink diluted in saline to 15 c.cm After a lapse of four days to allow for absorption of carbon pigment laparotomies were performed and the mesial quarter of the spleen removed for section After a further two days to allow for recovery from operation three of the rabbits were given by stomach tube 0·6 g sulphanilamide mixed with 10 c.cm acidulated water the other three as controls received the equivalent amount of acidulated water in the same way These doses were repeated daily for fifteen days after which each rabbit again received a further similar intravenous injection of india ink Doses of sulphanilamide or acidulated water were given on the sixteenth and seventeenth days and on the following day the rabbits were killed and the spleens removed for section The portions of spleen were cut at standard thickness and at right angles to the long axis of the organ Using a × 10 eyepiece and a one-sixth objective two hundred fields were examined for each section of spleen and the number of reticulo-endothelial cells containing carbon counted Some of these fields naturally contained Malpighian corpuscles whose size varied enormously and for that reason it was decided to neglect the count in any field which included a portion of a malpighian corpuscle in calculating the average number of reticulo-endothelial cells per field The results of this assay are set out in Table IV

TABLE IV

A.—*Rabbits (R) Receiving Sulphanilamide*

—	R 1	R. 2	R 3.
Total fields counted	200	200	200
Before sulphanilamide—			
1 Fields not containing malpighian corpuscles	140	155	164
2 Average number of reticulo endothelial cells per field	32·3	33·4	27·4
After sulphanilamide—			
1 Fields not containing malpighian corpuscles	107	140	173
2 Average number of reticulo endothelial cells per field	51·5	43·0	99·2
Percentage change	+50·4	+28·7	+26*

B —*Controls (R)*

—	R 4	R 5	R 6
Total fields counted	200	200	200
Before acidulated water—			
1 Fields not containing malpighian corpuscles	148	131	141
2 Average number of reticulo endothelial cells per field	33·6	28·0	22·5
After acidulated water—			
1 Fields not containing malpighian corpuscles	147	118	132
2 Average number of reticulo endothelial cells per field	30·3	25·1	23·5
Percentage change	−9·8	−12·3	+4·4

Before drawing conclusions from these results it has been borne in mind that two sources of error may be present Shrinkage of the tissue during processing may give an abnormally high value to the average number of cells per field in addition attention has been drawn by Cappell (1930) to the fact that animals with toxic symptoms may show an increased mobilisation of reticulo endothelial cells These two fallacies probably have some bearing on the abnormally high count found in the second assay for Rabbit 3

These experiments indicate that sulphanilamide stimulates the reticulo endothelial system although it is not clear whether it stimulates the production of phagocytic cells or the phagocytic activity of cells already present in the splenic reticulum Here it should be mentioned that the spleens of the rabbits that had received sulphanilamide contained numerous large masses of pigment included in clumps of cells : these masses were almost absent from spleens of control animals In another series of animals upon which daily white blood-cell counts were made and which at the same time received daily doses of sulphanilamide no significant change in the percentage or total number of large mononuclears was detected. Hence it is highly probable that the action of sulphanilamide upon the reticulo-endothelial system is in the nature of a direct stimulation of the phagocytic properties of the individual cells.

SUMMARY

1 The bacteriostatic action of sulphanilamide upon hæmolytic streptococci is preceded by a phase of growth stimulation

2 The growth stimulation is more conspicuous in young cultures than in cultures that have passed through the logarithmic phase of growth

3 Sulphanilamide is more soluble in the fatty envelope which can be separated from hæmolytic streptococci than in aqueous solution. The significance of this with regard to its stimulatory and bacteriostatic actions is discussed

4 Sulphanilamide does not appear to modify the activities of polymorphonuclear leucocytes

5 Sulphanilamide stimulates the phagocytic activity of reticulo-endothelial cells of rabbits The significance of this with regard to its action in infections of human subjects has not been investigated

6 Sulphanilamide stimulates the production of polymorphonuclear leucocytes by the bone marrow in rabbits

7 Attention is drawn to certain minor toxic effects of the drug

In conclusion we wish to express our thanks to Messrs Bayer Products Ltd for kindly supplying us with the drug

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ELECTROCARDIOGRAPHIC CHANGES OF A T$_3$ PATTERN IN PERICARDIAL LESIONS

AND IN STAB WOUNDS OF THE HEART

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IN cases of acute myocardial infarction serial electrocardiograms show characteristic changes that are now well recognised. These changes are temporally divided into an early and a late phase. In the early phase, during the first few days, there is elevation of the R–T segment with or without an upright T peak; in the late phase which commonly lasts for weeks or for months the R–T segment has an iso-electric origin, is often upwardly convex, and runs into a sharply inverted T peak. The two phases frequently overlap.

Such changes are often referred to as being of a coronary type, or they are called "coronary T waves." They commonly occur either in leads I and II or in leads III and II, and are most marked in lead I or in lead III respectively. In the former case the coronary T wave is said to be of the T$_1$ type, and in the latter it is of the T$_3$ type. Infarction of the anterior apical part of the left ventricle from occlusion of the anterior descending branch of the left coronary artery gives rise to the T$_1$ type; infarction of the posterior basal part of the left ventricle from occlusion of either of the circumflex arteries, usually the right, gives rise to the T$_3$ type. Isolated infarction of the right ventricle does not occur. An important feature of these electrocardiograms is the reciprocal behaviour of the S–T segment in lead III in the T$_1$ type and in lead I in the T$_3$ type. Thus in the former there is commonly depression of the S–T segment in the early phase, and a sharply upright T peak in the late phase. These features have been fully described by Parkinson and Bedford,[22] by Pardee,[21] and by Barnes and Whitten.[3]

So called coronary T waves have also been described in cases of pericarditis with and without effusion, in cases of hæmopericardium, and of stab wound of the heart surgically repaired. Little distinction has been drawn between the behaviour of the R–T segment in these conditions and its behaviour in cases of myocardial infarction. It is the purpose of this paper to show that there may be a difference, and that there is an electrocardiographic pattern which is characteristic of pericardial lesions.

EFFECTS OF PERICARDIAL TAMPONADE

From the clinical and experimental studies of Scott, Feil, and Katz,[31 32] Clowe, Kellert, and Gorham,[6] Randles, Gorham, and Dresbach,[27] the Foulgers,[13] and of Bay, Gordon, and Adams,[5] it seems clear that a rise in intrapericardial pressure sufficient to prevent proper filling of the heart—i.e., pericardial tamponade—causes a lowering of the voltage of Q R S, elevation and upward convexity of the R–T segment, and inversion of the T wave, these changes commonly occurring in all three leads and especially in lead II. It seems equally clear that the changes are reversible when the tamponade effect wears off. These conclusions are supported by the clinical studies of Scherf,[28] of Harvey and Scott,[14] and of Purks.[26]

Cases of pericarditis apparently without effusion have been studied electrocardiographically by Porte and Pardee,[23] Fitzgerald Peel,[12] Padilla and Cossio,[20] and by Holzmann.[17] From these studies it may be concluded that in cases of pericarditis R–T changes may be temporally divided into two phases, early and late. In the early phase there may be elevation of the R–T segment, and in the late phase there may be inversion of the T wave with or without upward convexity of the R–T segment. The important feature of these changes is that they occur in all three leads and especially in lead II. It must be observed however that a small pericardial effusion, indetectable clinically, may cause a high intrapericardial pressure if its accumulation is sufficiently rapid, and that therefore the above evidence is not conclusive.

Herrmann and Schwab[15] experimented with ten goats, and confirmed the work of the Foulgers on the effects of pericardial tamponade. Elevation of the R–T segment occurred in all leads, but more striking and more frequent was inversion of the T wave with upward convexity of the R–T segment. Their injection fluid consisted of protein, blood, or bacterial or sand suspensions, fluids calculated to produce a pericardial reaction. As the tamponade effect wore off—owing to stretching of the pericardium—later electrocardiographic changes commenced. The R–T origin became iso-electric and the T waves became inverted in all leads. In 1935 the same authors[30] reported the electrocardiographic changes in a group of 7 cases of pericarditis of mixed ætiology. A sufficient number of serial records was a feature of this study. They concluded that elevation of the R–T segment was especially a feature of tamponade, and was therefore seen early with rapidly developing effusions; that it usually occurred in all leads, and if only in leads I and II there was never reciprocal depression of the S–T segment in lead III—as is commonly seen in cases of myocardial infarction; and that later changes were seen after the first week, and consisted of inversion of the T wave in all leads. They considered that this later change, which lasted for several weeks or even for months, was due to a process of organisation and repair in the epicardium and in the subepicardial myocardium.

In a recent article on tuberculous pericarditis Harvey and Whitehall[13a] report S–T changes somewhat at variance with those described in this paper. They find that the changes commonly occur in leads I and II, and that reciprocal depression of the S–T segment occasionally occurs in lead III.

ACCOUNT OF CASES

The present report deals with a group of 13 cases of pericardial disease of various kinds: 5 were rheumatic, 2 malignant, 2 streptococcal, 1 tuberculous, 1 a case of hæmopericardium from a ruptured heart, and 2 were cases of chronic constrictive pericarditis. Serial electrocardiograms showed characteristic changes in all instances. Significant elevation of the R–T segment occurred twice; upward convexity of the R–T segment also occurred twice; flattening or inversion of the T wave was seen in every case; and the changes described occurred in all leads and especially in lead II. In the cases showing elevation of the R–T segment pericardial tamponade was present in one and was not excluded in the other. The other changes occurred in cases with or without pericardial effusion. In cases with effusion however the voltage of Q R S increased as the fluid was absorbed. The ætiology of the pericardial lesion did not influence the findings.

The important feature of the electrocardiographic changes is their occurrence in all three leads and especially in lead II. They may be described as being of a T_2 pattern which serves to distinguish them from similar changes resulting from myocardial infarction where they are commonly of a T_1 or of a T_3 type as already mentioned Examples of this T_2 pattern are shown in Figs 1–4

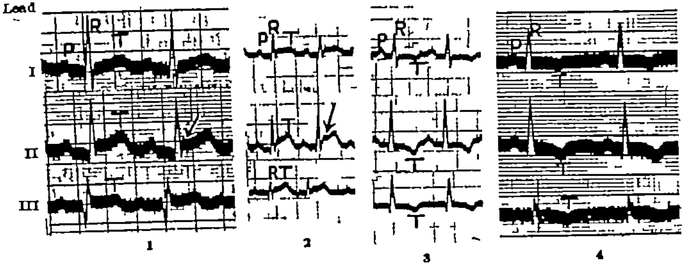

FIG 1.—Acute rheumatic pericarditis Tamponade not excluded. T_2 pattern, early phase
FIG 2—Hæmopericardium. T_2 pattern; early phase
FIG 3.—Tuberculous pericarditis with effusion proved by paracentesis and guinea pig inoculation T_2 pattern late phase
FIG 4—Malignant pericardial effusion carcinoma of bronchus infiltrating pericardium proved at autopsy T_2 pattern late phase

The following case is reported in detail because it illustrates the importance of recognising this pattern

The patient a man aged 53 was first seen by me on Sept 20th 1935 He complained of substernal pain of effort the characteristics of which were diagnostic of angina pectoris. There was moderate elevation of the blood pressure a skiagram showed little enlargement of the heart and an electrocardiogram was normal Full investigations yielded no additional positive information. The diagnosis was angina pectoris from occlusive coronary atheroma

He improved temporarily but on Jan. 12th 1936 he was readmitted to the Hammersmith Hospital with acute myocardial infarction The signs and symptoms were typical, and an electrocardiogram showed classical changes of the T_1 type (Fig 5 A) His course was satisfactory and he was discharged on March 5th 1936

On April 8th 1937 he was examined at an out-patient follow up clinic. In the meantime and against advice he had been working hard as a navvy and in the week ends he often undertook heavy gardening He had been free from symptoms except that after walking 10 miles on a few occasions he developed mild angina Examination revealed little His blood pressure was still 190/100 mm. Hg to which it had returned after his attack of January 1936 An electrocardiogram was perfectly normal (Fig 5 B)

Final admission.—On April 16th only a week later he was readmitted with a three-day history of severe substernal pain which had begun during the night and had awakened him Deep breathing aggravated the pain. He looked ill grey and a little cyanosed He was afraid to breathe deeply on account of the pain despite an injection of morphine gr ¼ He preferred being propped up but was not distressed when lying flat His temperature was 101 F and his pulse-rate 130 regular There was no evidence of systemic venous engorgement the liver was just palpable but not tender and there was a trace of oedema of the legs There were a few bilateral basal râles to be heard in the lungs. The heart sounds were rather faint there was gallop rhythm, and there was a pericardial friction rub The blood pressure had fallen to 130/90 mm Hg and there was a leucocytosis of 15 000 per c mm. with 82 per cent of polymorphs. The clinical diagnosis was acute myocardial infarction and he was treated by absolute rest and repeated injections of morphine

An *electrocardiogram* taken on the day of admission showed elevation of the R–T segment in all leads and especially in lead II (Fig 5 C) This was a typical T_2 pattern early stage and a diagnosis of ruptured heart with hæmopericardium was suggested. Confirmatory clinical evidence was not forthcoming The clinical features were consistent with an acute myocardial infarction alone and percussion of the cardiac borders did not suggest pericardial effusion

Three days after admission on the 6th day of the illness auricular flutter developed with a ventricular rate of 190 This was promptly controlled by intravenous digoxin. His condition seemed to improve and it was hard to believe that he had a ruptured heart On the 9th day of the illness his rhythm returned to normal and an electrocardiogram again showed elevation of the R–T segment in all leads and especially in lead II Ruptured heart with hæmopericardium was again suggested and another search was made for confirmatory clinical evidence The temperature was now normal the pulse-rate 90 respiration rate 25 and the blood pressure 125/75 mm Hg The pulse was small but not paradoxical. The heart sounds were faint and pericardial friction had given place to pleural friction. Percussion of the cardiac borders was repeated frequently but did not suggest pericardial effusion. There was however considerable emphysema An impaired percussion note at the left base and a frequent dry paroxysmal cough were the only suggestive clinical features On the 10th day of his illness the patient died suddenly He came to autopsy with the clinical diagnosis of acute myocardial infarction and with a suggested electrocardiographic diagnosis of hæmopericardium with tamponade due to cardiac rupture

Autopsy revealed a large hæmopericardium surrounded by a greatly thickened fibrinous pericardial sac A perforation was found through a recent infarct at the base of the left ventricle posteriorly The fibrin scraped off the heart weighed 50 grammes and the heart itself 425 g The right circumflex coronary artery was thromboсed giving rise to

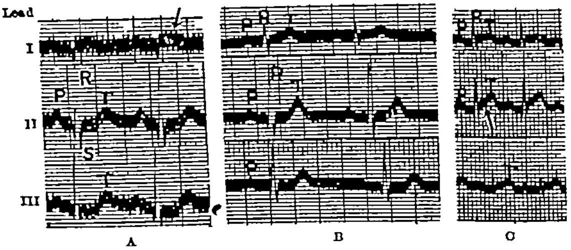

FIG. 5.—Man aged 53 (A) Jan 1st 1936: acute myocardial infarction Classical T_1 type (B) April 9th 1937 four days before cardiac rupture. Normal electrocardiogram. (C) April 18th: five days after cardiac rupture Hæmopericardium. Typical T pattern; early phase

the infarct at the base There was also an old white fibrous infarct at the apex of the left ventricle anteriorly, and there was severe occlusive coronary atheroma In addition there was considerable emphysema of the lungs and there was moderate passive venous congestion of the viscera

The case illustrates the diagnostic and prognostic value of recognising electrocardiographic changes of the T_2 pattern

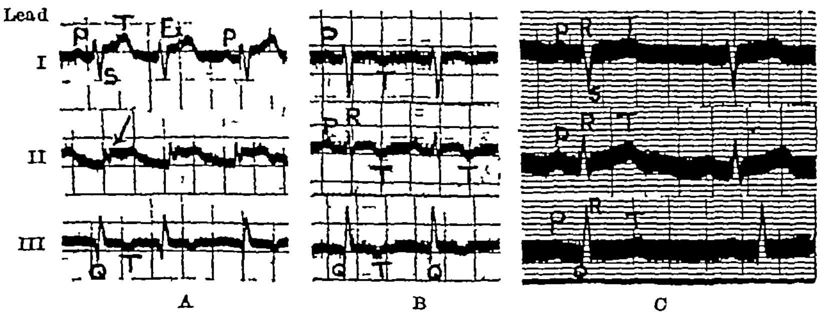

FIG 6.—Case of stab wound of right ventricle (Gissane 1937) (A) Second day Hæmopericardium T_2 pattern, early phase (B) Three weeks later T_2 pattern late phase (C) Six months later Normal T waves

VENTRICULAR STAB WOUNDS

Another group of cases must now be considered in respect of the electrocardiographic changes produced—cases of stab wound of the heart In 1935 Koucky and Milles [19] collected 8 such cases already reported and added one of their own From an analysis of these 9 cases they concluded that the electrocardiographic changes were due to myocardial injury and that they were of similar character whether the wound was in the left or in the right ventricle, and whether the anterior descending branch of the left coronary artery was ligated or not The electrocardiograms showed initial elevation of the R–T segment and subsequent inversion of the T wave, appearances commonly seen following myocardial infarction Davenport and Markle,[9] influenced by the work of Katz, Feil, and Scott,[33] were more inclined to regard the changes as an effect of pericardial tamponade

A recent case of stab wound of the heart, surgically repaired by Gissane, and reported in THE LANCET of July 17th, 1937, afforded an opportunity for serial electrocardiographic study (Fig 6 A, B, and C) This case and 13 others collected from the literature [4 8 11 16 19 24 25 29 33] have been analysed and are presented in the Table It is concluded that early changes, occurring within the first few days, consist of an elevation of the R–T segment, and that subsequent changes, which may last a month or two, consist of inversion of the T wave with or without upward convexity of the R–T segment The electrocardiogram finally returns to normal.

It is also evident that when the wound is situated in the anterior part of the left ventricle towards the apex, or if the anterior descending branch of the left coronary artery has been ligated, the electrocardiographic changes are usually of the classical T_1 type, and are therefore almost certainly directly due to the myocardial injury But when the wound is situated in the anterior part of the right ventricle the electrocardiograms conform to the T_2 pattern described in the earlier part of this paper In the early phase there is elevation of the R–T segment, and in the late phase inversion of the T wave, the changes occurring in all three leads and especially in lead II It is obvious that these changes may be due to hæmo-

VENTRICULAR STAB WOUNDS

Reference	Author	Position of wound	Ant desc branch of L coronary artery ligated	Post operative pericardial effusion	Post-operative pericarditis	Electrocardiograms										Inversion of T_3 in final normal electrocardiogram
						Early phase (1st week)					Late phase (2nd week–2nd month)					
						R–T elevation in lead—			Q large in lead—	Low voltage in lead—	Inversion of T in lead—			Q large in lead—	Low voltage in lead—	
						I	II	III			I	II	III			
10	Davenport and others	L V	Yes	?		+ +	+	R–T take-off iso-electric	III	III	+ +	+	Upright T wave	—	III	No
24	Porter and Bigger	L V	No	?		+ +	+ +	S–T take off depressed	—	—	+	+	Upright	—	—	No
4	Bates and Tallov	L V	No	Yes		+ + +	+ + +	Iso	I	III	+ + +	+ + +	+	III	III	Yes
11	Elkin and Phillips	L V	No	Yes							+ +	+ +	+	—	—	Yes
16	Holubec	L V	No	?							+	Diphasic	Upright	—	I	
11	Elkin and Phillips	R V	Yes	Yes	Frict rub	+ + +	+ +	Depressed	—	—	+	Upright	Upright	—	—	No
25	Purks	R V	Yes	?		+ + +	+ + +	Depressed	—	—	+ +	Diphasic	Upright	—	—	No
8	Davenport	R V	Yes	No							+ +	+ + +	+ +	II III	I	No
29	Schlomka	R V		?		Iso	+ Very sl	Iso	III	III	+	+ +	+	—	III	
24	Porter and Bigger	R V	No	?		+ +	+ +	+ +	—	I	+	+ +	+	I	—	No
33	Warthen	R V	No	?	Frict rub	+	+	Iso	I II	—	Upright	Diphasic	+ +	I II	—	No
19	Koucky and Milles	R V	No	Yes	Yes	+ +	+ +	Iso	—	III	+	+ +	+	—	III	No
9	Davenport and Markle	R V	No	Yes		+ +	+ + +	+ +	—	III						No
	Gissane's case	R V	No	Yes		+	+ +	Iso	III	II	+	+ +	+	III	II	No

pericardium which is an essential complication of all these cases The alternative explanation is that anterior right ventricular injury gives rise to electrocardiographic changes of the T_2 pattern There is little evidence for or against this point Isolated anterior right ventricular myocardial infarction does not occur clinically [1, 18] but in the cat Crawford and others [7] showed that experimental cauterisation of the anterior part of the right ventricle produced no electrocardiographic changes when the lesion was basal, or slight changes of the T_1 coronary type when the lesion was apical. Their findings with lesions in other situations fitted well with current knowledge concerning the relationship of the R–T changes to the site of myocardial injury in the human heart. Thus posterior basal left ventricular lesions produced changes of the T_3 type and anterior apical left ventricular lesions produced changes of the T_1 type What evidence there is therefore favours the view that *in cases of anterior right ventricular* stab wound surgically repaired the electrocardiographic changes produced are due to the associated hæmopericardium

CONCLUSIONS

1 Cases of pericarditis with or without effusion and of any ætiology and cases of hæmopericardium may give rise to electrocardiographic changes qualitatively similar to those produced by myocardial infarction

2 Pericardial T waves may however be distinguished from coronary T waves by recognition of the T_2 pattern which is characteristic of the former and which is in contrast to the T_1 and T_3 types of the latter

3 In cases of left ventricular stab wound electrocardiographic changes are usually of the T_1 coronary type and are probably due to the myocardial injury

4 In cases of right ventricular stab wound electrocardiographic changes are usually of the T_2 pattern and are probably due to hæmopericardium

I wish to thank Sir Frederick Menzies, chief medical officer of the London County Council for his kind permission to publish this material and Mr W Gissane for giving me the opportunity of investigating his case of stab wound of the heart by means of serial electrocardiograms.

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(*Continued at foot of next column*)

EFFECTS OF THE THYROTROPIC HORMONE OF THE ANTERIOR PITUITARY IN MAN

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DURING the last few years experimental work on the physiology of the anterior pituitary hormones has advanced very rapidly, and it seems imperative to demonstrate that their action in man is the same as in the lower animals The presence in the anterior pituitary gland of a substance capable of stimulating the thyroid has been recognised for a long time and the properties of this thyrotropic hormone have been studied considerably in animals with crude preparations but preparations suitable for use in clinical medicine have only recently become available There is now no doubt that in normal animals the *thyrotropic hormone can stimulate the thyroid gland to* greater activity In hypophysectomised animals the thyroid becomes inactive and repair of thyroid function can be effected by anterior pituitary implants *or by injections of thyrotropic hormone* These changes can be observed directly by examination of the gland itself or indirectly by observations on the basal metabolic rate which runs parallel with the *degree of thyroid activity (Collip 1935)* In animals therefore the thyroid gland is dependent on constant stimulation by the thyrotropic hormone of the anterior pituitary gland for its normal activity and variations in the secretion of the thyrotropic hormone regulate the changes in thyroid activity under physiological conditions

To show that the pituitary controls thyroid function in man and thus demonstrate the essential similarity of the pituitary and thyroid mechanisms in man and in animals it is necessary to prove three main points —

1 That the human thyroid gland can be stimulated by the administration of thyrotropic hormone

2 That the human thyroid ceases to function after destruction or removal of the anterior pituitary gland

3 That repair of thyroid function can be effected in man after hypophysectomy by replacement therapy with thyrotropic hormone

If these three points can be proved one can proceed further and investigate the relation of the thyrotropic hormone to disorders of the thyroid gland such as myxœdema, and Graves's disease. It is generally agreed that in Simmonds's disease (Graubner 1925) in which the pituitary ceases to function the human thyroid atrophies but exact data on this matter are unusually scanty Obviously in patients one cannot inspect the thyroid gland surgically or frequently remove pieces for section It is therefore necessary to measure the thyroid activity indirectly by estimating the basal metabolic rate which has been shown experimentally to be directly proportional to the degree of thyroid activity

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Experimental Investigations

Patients were kept at rest in bed, and under the same conditions throughout the experiment. Complicating factors, particularly anæmia, were repaired before the period of observation was begun. Estimations of the basal metabolic rate were made twice weekly, and no experiments were undertaken until constant results were obtained. The thyrotropic hormone was prepared by extraction from the anterior pituitary glands of pigs. The activity of each batch was measured in Heyl Laqueur units,[1] so that dosages could be compared. The injections, which were given intramuscularly into the buttock were painless, and no local reactions, either immediate or remote, were observed at any time.

For the first experiment two men were chosen who showed no evidence of endocrine abnormality.

CASE I

One of them was given 1200 units of thyrotropic hormone daily for three days. There was a prompt rise in the basal metabolic rate from a basal level between minus 5 per cent and 0 to a maximum of plus 40 per cent on the sixth day after the first injection. The metabolic rate then slowly returned to the basal level during the next two weeks (Chart I).

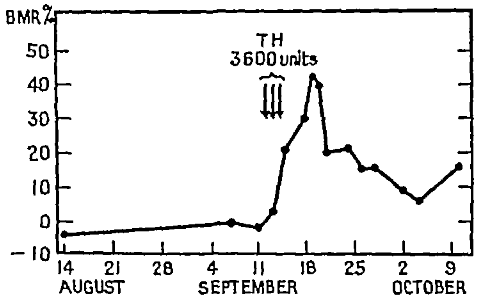

CHART I (Case 1).—Normal man. T H = Thyrotropic hormone.

CASE II

The second man was given smaller doses of hormone. He received daily injections of 400 units. In this case the rise in metabolism again occurred, but was more gradual. It rose from a basal level between minus 5 per cent and plus 4 per cent to plus 45 per cent after 12 injections. The treatment was then stopped, and the metabolism fell to the basal level during the next week.

PITUITARY INSUFFICIENCY

Next three patients were selected whose pituitary glands had been destroyed by tumours, either in or near the pituitary gland itself.

CASE III

The first patient was a man aged 46, who had had curious attacks for the last 17 years. They usually occurred in the early mornings, and were prone to be severe when he got up early and had no food. The attacks consisted mainly of a feeling that he did not know where he was. He had occasional occipital headaches, which would often radiate towards the vertex. For the last two years the headaches had become more frequent and more severe. The eyesight had recently begun to fail and he noticed that he was becoming slower mentally. He thought that his face had become fuller.

On examination there were no obvious skeletal changes. His mentality was slow, his skin dry and cool, and he had bilateral optic atrophy. The blood pressure was 108/78 mm Hg. There was *persistent* bradycardia and hypothermia. Radiograms showed considerable enlargement of the pituitary fossa with erosion of the posterior clinoid processes. The basal metabolic rate was minus 30 per cent.

He was given 10 daily injections of 400 units of thyrotropic hormone, and the basal metabolic rate rose progressively to a level of plus 9 per cent on the tenth day. The clinical change during this time was easily noticeable. The bradycardia and hypothermia disappeared, the skin became warm and smooth, and his cerebration improved. After cessation of the injections, the basal metabolism slowly fell to a low level again.

Craniotomy was performed, and a tumour was found occupying the pituitary fossa, and extending out under the right optic nerve, pulling the whole of the optic chiasm across with it. As much of the tumour was removed as possible. Histological sections of this tumour showed the characters of a craniopharyngioma. The patient died a few days after operation, and at autopsy the pituitary destruction was verified, and no damage to the overlying brain was found.

CASE IV

The second patient was a woman, aged 46, who for two years had had complete amenorrhœa, which she ascribed to an early menopause. For the last year she had been having pain in both eyes, and during the last few months had noticed a gradual failure of vision. She had occasional frontal headaches, but they were never severe. On examination at that time there were no skeletal changes. She had bilateral optic atrophy with a bitemporal hemianopia. A radiogram showed considerable enlargement of the pituitary fossa. Craniotomy was attempted, but had to be abandoned owing to the low blood pressure. For the next six months her sight improved temporarily, but she became slower mentally, and then her sight began to get worse again. On re-examination there was still no skeletal change, but her skin had become dry and harsh, her eyebrows were thinned, and she had developed a diffuse brownish pigmentation. She also showed persistent bradycardia and hypothermia. Her blood pressure was 95/70 mm Hg. There were no myxœdematous deposits. In view of the bad general condition and low blood pressure further operation was not performed.

The basal metabolic rate was found to be minus 40 per cent. She was given daily injections of 400 units of thyrotropic hormone. After thirteen injections the metabolism had risen to minus 4 per cent. It was then impossible to continue, as the patient was becoming less lethargic and very intolerant of interference. After cessation of injections the metabolism slowly fell down to the basal level. The pulse rate and temperature became normal for a few days at the height of the response, but rapidly returned to their previous low level as the metabolism fell.

CASE V

The third case was a man aged 23, who during the last two years had developed attacks of severe frontal headache often associated with vomiting. The attacks had become progressively worse recently, and he began to notice diplopia and failure of vision particularly in the right eye. On examination he was lethargic, but could be roused easily. There were no skeletal changes. The skin was dry and scaly, but there was no myxœdema. The beard was scanty and the eyebrows thinned. The genitalia were normal. The blood pressure was 120/80 mm Hg. The pulse rate was normal, but there was persistent hypothermia. The right eye was slightly proptosed, and there was complete blindness in this eye. The pupil was large and inactive, and the movements were almost nil. The left eye showed loss of the temporal field of vision and early optic atrophy. A radiograph of the pituitary fossa showed complete destruction of the bone forming the fossa.

The basal metabolic rate was minus 45 per cent. He was given eight daily injections of 600 units of thyrotropic hormone, and the basal metabolism rose to minus 1 per cent During this time he became more alert the pulse rate rose and the temperature became normal (Chart II)

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[1] One guinea pig unit of Heyl Laqueur is half the daily dose that, injected intraperitoneally on two successive days, induces a given degree of thyroid epithelial development in at least 60 per cent. of the test animals within 48 hours of the first injection.

The pituitary fossa was then explored and a tumour was found lying in the roof of the right orbit and surrounding the right optic nerve It also extended down through the diaphragma sellæ and had destroyed the pituitary gland The tumour was removed as completely as possible and proved to be a neuroblastoma

From these observations it is clear that in man the thyrotropic hormone is capable of stimulating the thyroid gland to greater activity In these cases with pituitary destruction the thyroid had markedly diminished or even ceased to function, and repair of thyroid activity was effected by administration of thyrotropic hormone. Thus it was demonstrated that the relation of the anterior lobe of the pituitary gland and the thyroid is the same in man as in the lower animals.

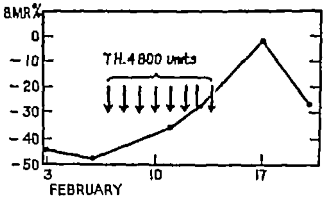


CHART II (Case 5).—Destruction of pituitary by neuroblastoma. T H. = Thyrotropic hormone

HYPOTHYROIDISM

If thyroid hypofunction in man can be caused by failure of adequate stimulation from the anterior pituitary it might be suggested that some cases diagnosed as hypothyroidism or myxœdema and showing no evidence of gross pituitary destruction might nevertheless be due to a simple failure of pituitary secretion. Such cases should respond to thyrotropic hormone whereas thyroid hypofunction arising from a local thyroid lesion should not respond and the thyroid secretion should need to be replaced by thyroid medication.

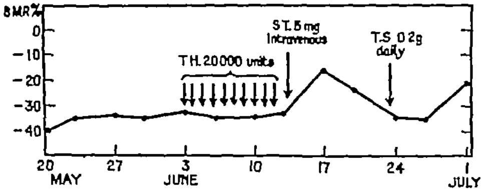
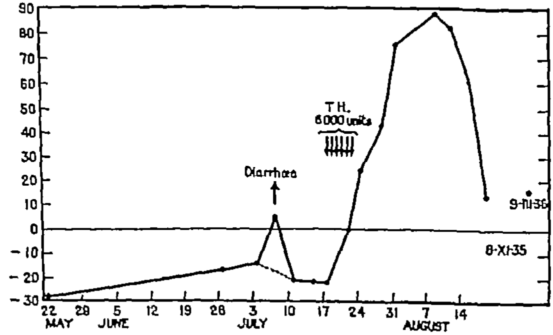


CHART III.—Patient with myxœdema T.H = Thyrotropic hormone. S.T = Sodium thyroxin. T.S. = Thyroideum siccum orally

Six patients with classical myxœdema were studied from this point of view Several of them had a severe anæmia, which was associated with menorrhagia. This anæmia was repaired before any experiments were begun. No patients were included in this group unless they had true myxœdematous deposits All had a low basal metabolic rate varying from minus 25 to minus 40 per cent They were given injections of thyrotropic hormone in daily doses for 10 days The total dosage ranged from 2400 to 20 000 units In none of these patients was there any significant rise in the basal metabolic rate They were then given 5 mg of sodium thyroxin intravenously following which they all showed a prompt rise in metabolism from 10 to 20 per cent This response was allowed to subside and thyroideum siccum given by mouth There was another rise in metabolism but more gradual than with thyroxin (Chart III)

It is obvious therefore that classical myxœdema does not respond to thyrotropic hormone and behaves as if it were a local lesion of the thyroid gland. Occasionally however patients are seen who show hypothyroidism without myxœdema and whose symptoms are similar to the condition seen in pituitary destruction with mental slowness, dry cold skin, bradycardia hypothermia and in women, disturbance of menstruation. Even though no evidence of gross pituitary destruction can be demonstrated in these patients the clinical picture suggests that the anterior pituitary is failing to stimulate the thyroid and that treatment with thyrotropic hormone might correct this condition



[CHART IV (Case 6).—Hypothyroidism without myxœdema. T.H = Thyrotropic hormone.

CASE VI

A man who showed this condition was investigated (Snapper and others 1937) He was aged 44 He was apparently robust and healthy until the age of 18 when he had a prolonged illness with diarrhœa and vomiting He was incapacitated for one year After this he apparently improved and was fit enough to join the army during the war But in France he had another severe attack of diarrhœa which was called dysentery Following this he developed a severe dyspepsia An abdominal exploration was performed, and owing to dilatation of the duodenum, a duodeno jejunostomy was performed He was relieved at the time but has had recurrent attacks of dyspepsia ever since He has become very constipated and has frequent bleeding from piles. For many years he had noticed that he was getting slow and lethargic, his hair had been falling out, and shaving became less frequently necessary Recently he began to get very breathless on exertion, and to have severe palpitations, often with marked precordial discomfort

On examination he was extremely pale The skin was dry and cool There was marked frontal and occipital alopecia, and the eyebrows were thinned on the outer sides The beard was scanty, the axillary hair absent, and the pubic hair poorly developed and of feminine distribution He was very slow mentally, and in all his movements His temperature was subnormal, but his pulse rate was normal He was severely anæmic and had achlorhydria to histamine This was treated with iron and the anæmia was repaired The piles were injected and the loss of blood ceased The repair of the anæmia lowered the pulse rate and improved his cardiovascular symptoms, but there was no effect on his other conditions The basal metabolic rate now varied between minus 14 and minus 30 per cent He was given six daily doses of thyrotropic hormone, making a total dosage of 6000 units Following this, there was a dramatic change in his condition His skin became warm and moist, he developed a fine tremor of the hands, and in contrast to his former lethargy he became nervous and excitable, and at times very restless The thyroid gland became slightly swollen, and a systolic bruit became audible over it The basal metabolic rate rose rapidly and continued to rise for three weeks, reaching a maximum of plus 88 per cent The reaction then slowly subsided, and the metabolic rate fell during the next ten days to 12 per cent (Chart IV)

Discussion

From the evidence it is justifiable to conclude that the thyroid gland in man is under the control of the anterior pituitary gland In the absence of stimulation from the pituitary, thyroid function ceases and variations in the amount of stimulation by the thyrotropic hormone regulate the degree of thyroid activity The hormone thus provides a valuable weapon for deciding in any case of hypothyroidism, whether the hypothyroidism is secondary to failure of the pituitary or is a primary thyroid failure Cases of hypothyroidism can be then classed into two main groups In the first variety or true myxœdema, whether spontaneous or from thyroid removal, no response can be obtained by giving thyrotropic hormone, and replacement therapy with thyroid itself must be used This observation is interesting, since it has been shown that in some cases of myxœdema there may be excessive amounts of thyrotropic hormone circulating in the blood

There is a second and much smaller group of patients who show hypothyroidism, without the pathognomonic sign of myxœdema, the infiltration of the subcutaneous tissues They have mental retardation, associated with alopecia and dryness of the skin bradycardia and hypothermia, and the clinical picture resembles pituitary destruction, and suggests a primary pituitary failure with secondary thyroid hypofunction This has been shown to be true of the patient recorded here, since a marked response could be obtained by the use of thyrotropic hormone, which could not be obtained in cases of frank myxœdema in whom the lesion is presumably in the thyroid gland itself

The position of hyperthyroidism is not yet clarified and apart from the association of thyrotoxicosis with active acromegaly, no suggestion has been found that an increased secretion of thyrotropic hormone occurs in Graves's disease In fact such observations as have been made in man suggest the reverse, that there are smaller amounts of hormone present in the blood and urine than normally

In animals following prolonged treatment with thyrotropic hormone the thyroid ceases to overact, returns to a resting state, but shows no evidence of exhaustion (Scowen and Spence 1936) There must therefore have developed a mechanism for protecting the thyroid from excessive stimulation. Apparently a substance is produced which inhibits the action of the thyrotropic hormone (Collip and Anderson 1934, Scowen and Spence 1936) This is called an antihormone It is not yet certain whether this be an exaggeration of a normal hormone antihormone balance, or a response to foreign material injected with the hormone It seems unlikely that an animal would develop a true antibody to its own hormone, since this would render it valueless to the organism, though an antibody might be formed in response to a hormone prepared from a different species But, if one considers that there is normally a balance between hormone and antihormone, failure of production of antihormone would make the thyroid and possibly other structures more susceptible to the action of smaller concentrations of thyrotropic hormone

It is interesting to note that exophthalmos can be induced in animals by injections of thyrotropic hormone, even when the thyroid is no longer overactive or has even been removed (Loeb and Friedman 1932, Marine and Rosen 1934, Schockaert 1932) This fits well with the clinical observation that exophthalmos may progress or even develop for the first time after thyroidectomy in Graves's disease

Apart from cases of pituitary insufficiency, it is doubtful whether there be any therapeutic indication for the use of thyrotropic hormone in man, as hypothyroidism can be corrected, and the metabolism accelerated more simply, more cheaply, and perhaps more safely, by the administration of thyroid extract Nevertheless, more knowledge must be obtained from human material of the actions of the thyrotropic hormone and its behaviour in health and disease The question of the production of antihormones in man must also be investigated, for as yet such substances have only been found in animals, and the final proof that they have any bearing on the practice of medicine must rest on observation in man

Summary

Thyrotropic hormone prepared from the anterior pituitary gland of the pig raised the metabolic rate in man in health and in cases of pituitary insufficiency, but was without effect in myxœdema

My thanks are due to Prof L J Witts and Prof J Paterson Ross for the facilities which they have given me I am grateful to Dr A. N Macbeth of Organon Laboratories and Prof Schoeller of Schering Ltd for supplies of anterior pituitary material

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WORLD-WIDE MALNUTRITION —Speaking in the second committee of the League Assembly at Geneva on Sept 22nd Mr Robert Bernays parliamentary secretary of the Ministry of Health, referred to the extent of malnutrition outside Europe In India he said, there were probably millions of people who could not afford more than one meal a day, in China, according to the Chinese Government, "most Chinese are in a state of malnutrition all the time" and from his own personal experience this spring he could emphasise how acute there was the problem of undernourishment in tropical Africa

CLINICAL AND LABORATORY NOTES

ACUTE INFECTIVE ENDOCARDITIS DUE TO BACTERIUM COLI

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WELL-AUTHENTICATED cases of infective endocarditis caused by *Bacterium coli* are sufficiently uncommon to warrant description of a single example

A girl aged 18 was admitted to the Cardiff City Isolation Hospital on April 22nd 1937 as a case of typhoid fever It was subsequently elicited that two years earlier she had had an illness simulating chorea She had been ill since April 15th with headache shivering repeated vomiting and obstinate constipation. The day before admission her serum gave O agglutination to 1/50 but no H agglutination with *Bacterium typhosum* and no agglutination with the paratyphoid organisms

On admission she complained of severe frontal headache and drowsiness Her temperature was 101 2 F pulse rate 122 respirations 26 The heart sounds were regular but the apical first sound was blurred. The fauces were injected and the tongue furred Nothing abnormal was felt in the abdomen.

Investigations and progress —Repetition of the Widal tests on April 26th showed no change The leucocyte count at this time was 13 000 per c.mm (polymorphs 69 per cent) By the 29th there was increased drowsiness a temperature oscillating between 100°–103 F and a well conducted apical systolic bruit A tentative diagnosis of infective endocarditis was made From April 30th onwards crops of petechial hæmorrhages appeared on various areas of the skin and in the conjunctivæ and the cardiac bruit grew more pronounced Four days before death the area of splenic dullness became definitely enlarged, and the previously swinging temperature dropped to normal She became very apathetic and exhausted incontinent of urine and fæces and died on May 10th Daily examination of the urine during her illness consistently revealed a trace of albumin and occasionally red blood-cells In spite of repeated attempts the causative organism was not recovered from the blood.

Pathology —At the post-mortem examination acute infective endocarditis was found The auricular surfaces of both cusps of the mitral valve were completely hidden by exuberant masses of deep red friable vegetations which almost occluded the valvular orifice and extended upwards on to the auricular walls and downwards over the chordæ tendineæ Microscopically the vegetations consisted of fibrin thrombus in which were embedded clumps of short or almost coccoid Gram negative bacilli There was acute inflammation of the mitral valve but no sign of old inflammation or other abnormality The kidneys contained many small pyæmic abscesses and in the lower pole of the left kidney there was a recent septic infarct In both the abscesses and the infarct were masses of Gram negative bacilli similar to those in the mitral vegetations The spleen was enlarged and rather soft The lungs showed an early broncho pneumonia. The mucosa of the cæcum and the ascending colon was congested and microscopically there was in some areas necrosis of the villi with scattered hæmorrhages in the submucosa

The whole of the skin surface the conjunctivæ, and the pleuræ and peritoneum were flecked with numerous deep red petechiæ The other organs were normal.

Bacteriology —A broth culture tube inoculated from the centre of one of the mitral vegetations gave a pure growth of a non motile Gram negative bacillus which consisted of short plump rods and almost coccal forms similar to those seen in the vegetations and in the kidney lesions On agar it produced after 24 hours low convex glistening grey colonies of a form commonly assumed by *Bact coli* On human and rabbit blood agar the colonies became surrounded after 24 hours with a zone of hæmolysis The organism gave a negative Voges Proskauer and a positive methyl red reaction it produced acid and clot in milk and reduced nitrates It failed to liquefy gelatin It fermented lactose glucose mannitol, and dulcitol with liberation of acid and gas It failed to ferment maltose saccharose insulin, salicin and adonite Culturally and biochemically therefore it fell into the group *Bact coli*

DISCUSSION

Cases of *Bact. coli* endocarditis are reported by Horder (1909) Norris (1911) Thayer (1926) Cowan (1926), Dickar (1932) Phipps (1932), Duhig (1933), and by Crawford and Cruickshank (1934)

Owing to the ease of contamination of tissues in the cadaver with coliform organisms we consider it essential that besides culture of the organism from the affected valve microscopic examination should reveal the abundant presence of a Gram negative bacillus in the vegetations Of the cases cited above only one case recorded by Horder two by Dickar one by Duhig and one by Crawford and Cruickshank satisfy these postulates and are admitted to discussion.

Dickar on the grounds that the organisms isolated from his cases failed to ferment saccharose dulcitol, and salicin, but fermented adonitol, classified them as *Bacterium acidi lactici*, which he regards as a species different from *Bact. coli* It has however long been recognised that different strains of *Bact coli* though similar in most cultural and biochemical properties vary in their power to ferment certain sugars and alcohols Topley and Wilson (1936) do not consider that minor differences of fermentative power justify the creation of separate species in addition to *Bact coli* They prefer to group commonly occurring strains with similar motility and fermentative powers as varieties within the species *Bact coli* so that according to their classification Dickar's two organisms have the characteristics of *Bact coli* var *acidi lactici*

Crawford and Cruickshank entitle their case Infective Endocarditis due to *Bact coli* ' and state that the organism isolated from the heart valve gave all the reactions of *Bact acidi lactici* They do not discuss its bacteriology but clearly consider it very closely related to *Bact coli* Duhig s organism falls exactly into the variety *Bacterium immobile* of Topley and Wilson. Bacteriological details of Horder's organism are not given The organism isolated from the present case though culturally and in most biochemical respects falling within the species *Bact. coli* does not exactly correspond in fermentative properties with any of the varieties tabulated by Topley and Wilson

A question worth consideration is the point of entry and original focus of infection in these cases of *Bact coli* endocarditis Jacob (1909) and Brian (1912) in two series of cases of *Bact coli* septicæmia without endocarditis found that the common sites of primary infection in descending order of frequency were the biliary tract the urinary tract the gastro intestinal tract and female genital tract Felty and Keefer (1924) whilst corroborating the importance of these sites rank genito-urinary infection at the head of the list Out of their 28 cases of *Bact. coli* septicæmia 20 had undergone surgical manipulation of the genito urinary tract All these authors record a small remnant of cases in which no primary focus coul

Of the cases of *Bact coli* septicæmia with endocarditis now under review, Duhig's had a pyelonephritis following pregnancy, one of Dickar's a prostatic abscess, which had been incised from the rectum, and the other cholecystitis, from all these foci an organism identical with that found in the heart valve was cultivated No primary lesion is mentioned in Horder's case Crawford and Cruickshank, on the grounds that their case had suffered from gastro enteritis and showed an inflamed but not ulcerated colon, suggest its mucosa as the portal of entry of the causative organism In our own case we consider the microscopic lesions in the colon mucosa to be secondary to the septicæmia, and the primary focus remains unascertained

Our special thanks are due to Dr W Parry Morgan, Cardiff City bacteriologist, for confirming the bacteriological findings

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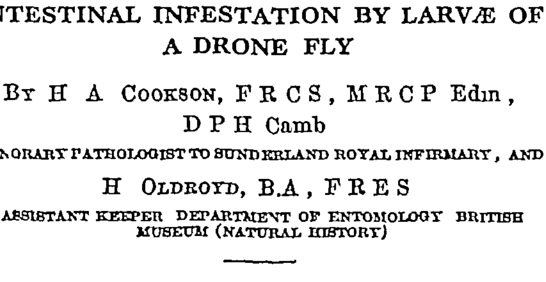
INTESTINAL INFESTATION BY LARVÆ OF A DRONE FLY

By H A Cookson, F R C S, M R C P Edin, D P H Camb
HONORARY PATHOLOGIST TO SUNDERLAND ROYAL INFIRMARY, AND
H Oldroyd, B.A, F R E S
ASSISTANT KEEPER DEPARTMENT OF ENTOMOLOGY BRITISH MUSEUM (NATURAL HISTORY)

A man aged 35 complained that he had noticed blood and a large number of " worms " in his motion Beyond some slight itching around the anus he was not inconvenienced in any way

He was a glazier by trade, but previously a sea going engineer He had made three trips abroad (dates not known), covering a period of 12 months in all, visiting India twice and the Black Sea once

Two years ago, in the summer of 1935, he passed, he says, two " worms " of the same kind as those passed during the present attack. On both occasions he was using a field latrine on a housing estate on which he was working, and thus saw the parasites easily Apparently there were no parasites noted in between the two occasions, and so far only on one occasion this year—namely, in the early days of August It was this that caused him to come under medical care He is a decent, intelligent man, earning a fair wage, and living in a good, working class district



Late larval (rat tailed') stage of Eristalis

The larva found in the stools was identified as a syrphid, one of the drone flies of the genus *Eristalis*, which breed in water containing a high proportion of manure or rotting matter of any kind It was well grown, but had not reached the adult stage, as has been known in some other forms of myiasis The illustration shows the " rat tail " characteristic of this stage of development

A number of cases of myiasis by drone fly larvæ have been recorded Austen (1910) mentions a woman who had come to this country recently, from France, and expresses the opinion that the infection was brought about by eating watercress Riley and Johannsen (1932), in their text book, state that Hall (1918) records 17 such cases, including that of a boy who drank from a ditch full of rotting material The most probable source of infection in all cases of this kind is the drinking of foul water containing the eggs or very young larvæ

The larvæ are saprophagous, and it is very unlikely they would attack living tissues The damage to the intestine resulting in the bleeding in the present case would be merely incidental to the passage of a large number of larvæ No doubt normal vermifuge treatment would be effective

Our thanks are due to Dr W A. Carruthers of Sunderland for permission to publish these notes about his case

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INTUSSUSCEPTION STARTING IN AN INVERTED MECKEL'S DIVERTICULUM

By Leonard Ley, M B, B Chir Camb
SURGEON TO GREAT YARMOUTH HOSPITAL NORFOLK

This case came under my care on August 27th.

The patient was a plump baby of five months, a girl She had been fed partly at the breast and partly on Nestlé s milk Pain and vomiting had begun 36 hours previously, and a motion had been passed with a little blood

When I saw the child she had been quiet, except for one attack of crying in the 1½ hours since admission to hospital The face was rather pinched, and an attempt to examine provoked crying I gave chloroform and felt a tumour which was less defined than I should have expected with so long a history Rectal examination showed the rectum to be full of soft fæcal material, no blood

On opening the abdomen I found an enterocolic intussusception reaching to the middle of the transverse colon It was reduced fairly easily, and proved to have an inverted Meckel's diverticulum as its apex This diverticulum had rather a broad base and was about half an inch in length In view of the infant's tender years and the long history, I decided to do no more The abdomen was closed in layers, and a perfect recovery followed

I propose to resect the diverticulum and remove the appendix, when and if the child is three or four years old

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Monmouth Hospital —Mrs J R Harding has opened a new casualty ward at this hospital

Worcester Royal Infirmary —Lord Nuffield is sending this hospital a further gift of £10,000 which he suggests might be used to provide beds for paying patients

REVIEWS AND NOTICES OF BOOKS

1 A First Course in Hygiene

Ninth edition By ROBERT A LYSTER, M.D Ch B B Sc. D.P H Lecturer in Public Health and Lecturer in Forensic Medicine at St Bartholomew s Hospital. London University Tutorial Press 1937 Pp 376 4*s* 6*d*

2. Health Education of the Public

By W W BAUER, B S M.D Director Bureau of Health and Public Instruction, American Medical Association; and THOMAS G HULL, Ph.D Director Scientific Exhibit, American Medical Association London W B Saunders Co 1937 Pp 227 12*s*

1 THE revision of an established text-book on hygiene intended for non medical students teachers nurses school visitors members of local government bodies and those generally who are interested in the public health is of topical interest in view of the national campaign inaugurated during the present week. The discussion of each topic is preceded by instruction in the anatomy and physiology of the system chiefly involved or in the physics and chemistry of the environmental mediums reacting on health and relevant experimental work is described While most of the subject matter has been brought well up to date some is disappointing There is no reference to the modern product of low temperature carbonisation among fuels accredited is classified with tuberculin tested milk as possibly exempt from the need of heat treatment the chemical constitution of vitamins is dismissed with a statement that it is not fully understood the variety of vitamins which come under the designation B is ignored; and the problems of infection and immunity are inadequately explained. Nevertheless, a very wide range of material is well covered, and the book which is copiously illustrated, should be useful to teachers who are equipped to supplement its information where necessary

2 The appearance of this book is also opportune It brings together the experience of two American scientists who have specialised for many years in the technique of health education, and are fully aware of the difficulty of securing a sustained interest in any sort of repetitive publicity They discuss each medium—wireless exhibits public addresses pamphlets the press the cinema personal correspondence, and other devices—assess its value and describe in detail the conditions of its successful use There are numerous illustrations While the book is intended for American readers those who are embarking on health education in this country will doubtless read it with profit though perhaps not always with agreement As it emanates from a medical organisation, it pays a proper regard to the ethics of professional participation in a health or any other campaign

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Evolution and its Modern Critics

By A MORLEY DAVIES D Sc lately Reader in Palæontology in the University of London London Murby and Co 1937 Pp 277 7*s* 6*d*

WHEN Dr Johnson took a turn through Scotland he went out of his way to visit Lord Marboddo who held that the ourang-outang was nothing less than a *man* who *had failed* to develop his capacity for speech. Since then a good deal of evidence has been accumulated from a variety of sources which has provided a convergent and consistent mass of probabilities convincing to most people of the truth of evolution. Some are however still refractory especially Mr Douglas Dewar and for their conversion Prof Morley Davies has written this eminently readable little book It is in no way a formal statement of the evidence but a rather gossipy discussion of some of the difficulties made by Mr Dewar and others the bulk of the data being as one would expect palæontological It will of course have no effect on those who do not believe in evolution: belief, including scientific belief depends on inclination rather than evidence Many believe in the theory of evolution because it has proved itself productive of new knowledge and if it ever loses that criterion of truth they will have no more confidence in it The readers to whom we would recommend this book are those who believe in evolution already and would like to know more about it

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Das Hormon des Corpus Luteum

Biologie Chemie und Klinik Von Dr ERICH FELS Dozent für Geburtshilfe und Gynäkologie Leipzig und Wien: Franz Deuticke 1937 Pp 169 M 12

THE author of this monograph has himself done original work on the hormonal action of the corpus luteum, and has also enlarged his experience by contact with a famous teacher Prof L Fraenkel His survey is timely in view of the isolation and laboratory preparation of progesterone the pure hormone The historical and physiological aspects of the subject are well described and the chapter on the chemistry of progesterone is written with the authority of Dr K. Slotta, one of the first to isolate the hormone The consideration of the clinical applications of the hormone is restricted to one chapter of thirty pages On one point we join issue with the author Fels and Slotta believe and are alone in their belief that the two interconvertible forms α progesterone and β progesterone differ slightly in their biological activity and that a mixture of the two forms is about twice as active as either separately Such an effect if it existed would be interesting and important but neither in this book nor elsewhere has there been published any theoretical support for the peculiar type of isomerism postulated a collection of animal assays statistically treated would be necessary to support the view put forward if it is to carry conviction. It is fair to add that here as elsewhere in this valuable monograph the arguments for and against the theory are impartially reviewed

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An Introduction to the Theory of Statistics

Eleventh edition By G UDNY YULE C.B E M.A F R S Fellow of St John s College and formerly Reader in Statistics Cambridge; and M G KENDALL, M.A. formerly Mathematical Scholar of St John s College Cambridge London Charles Griffin and Co 1937 Pp 570 21*s*

Mr Udny Yule s text-book, first published in 1910 was based upon the course of instruction he gave during his tenure of the Newmarch lectureship in statistics at University College London in 1902–09 It soon won a wide recognition, and for statistical workers it has become and remained an essential item of equipment, of which the value has not been lessened by the growing number of its competitors In ensuing editions some revisions were made and additional matter has from time to time been incorporated in supplements to cover recent advances in statistical methods But after twenty five years of productive life it seemed that the time had come when a complete revision should be undertaken This task Mr Yule was reluctant to undertake himself, believing, with customary modesty, that it would be better done by a younger man more in touch with recent literature and less affected by prejudices in favour of the old and familiar In Mr Kendall he has found an admirable collaborator, and the conservative reader will rejoice to note that, apart from the substitution of some numerical illustrations by newer ones, very little of the original material has been deleted The major changes lie in the additions made These include several new chapters on sampling, with an excellent introductory chapter to the statistical technique applied to small samples and the inferences that can be drawn from them Other new sections deal with moments and measures of skewness and kurtosis, with simple curve fitting by the method of least squares, and with interpolation and graduation Tables of various functions required in statistical work have been included at the end of the book The publishers have played their part by providing a larger page and a type which is a distinct improvement on the old In its new form this classic should long continue to be of service to all students of statistical theory and technique who are not daunted by algebraical formulæ

The Backward Child

By CYRIL BURT, M A , D Sc Oxon , Professor of Psychology in the University of London London University of London Press 1937 Pp 694 20*s*

Prof Burt makes it clear that backward children cannot be dealt with in the mass They have to be studied as individuals after an attempt has been made to assess the particular cause or (more usually) causes which have contributed to their condition His book provides a very complete equipment for investigation of individual cases, and describes methods of examination and testing in great detail, but his idea that teachers could carry out much of the work seems to us rather optimistic

In more than half the backward children investigated by Prof Burt in London and Birmingham the major cause of their state was dull intelligence Specific intellectual disabilities, temperamental peculiarities, sensory and motor defects, physical ill health, and social obstacles played only minor parts At least 70 per cent of the cases were definitely psychological in origin Bodily weakness and malnutrition were never more than contributing factors, and indeed the experience of experts seems to be that it is rare for physical treatment by itself to change a backward child into an average scholar, a fact worth noting Incidentally, Prof Burt discredits the myth beloved of speech day orators that great geniuses have been dullards at school The dull remain dull, all that can be said is that sometimes the accidentally backward make a better showing in after life than was anticipated

Prof Burt has given considerable attention to the vexed question whether a change from left- to right handedness tends to produce stammering He concludes that stammering mostly occurs in neurotic children, and that it is usually accompanied by other indications of nervous disturbance He is disposed to the view that the fundamental cause of disturbance is not the change of hand but the strain of substituting written words for spoken Permanent left handedness, he believes, results more from custom than from inherited compulsion, and a change should be effected early, best of all before speech begins Even at a later date, however, change to the use of the right hand is mostly safe if skilfully guided

On speech defects Prof Burt is equally illuminating Speech is a motor process, guided by cognitive control, motivated, and liable to be disturbed by emotion, all three elements must be considered in training children who stammer

Unlike some modern authorities, Prof Burt is a definite advocate of segregation for the backward child He believes separate classes or schools necessary in the interests of all concerned—a view contrary to that expressed in the recent circular issued by the Board of Education [1]

Surgery of the Sympathetic Nervous System

Second edition By GEORGE E GASK, C M G, D S O, F R C S Eng, Emeritus Professor of Surgery, University of London, Consulting Surgeon, St Bartholomew's Hospital, and J PATERSON ROSS, M S Lond, F R C S Eng, Professor of Surgery, University of London, Surgeon and Director of the Surgical Unit, St Bartholomew's Hospital London Baillière, Tindall and Cox 1937 Pp 191 16*s*

ABOUT ten years ago a great wave of enthusiasm for sympathetic denervations spread to this country from foreign parts It brought with it operations for almost innumerable conditions, and its subsidence has left some of these high and dry, and has removed others completely Some surgical procedures have neither been generally accepted nor rejected as valueless, and guidance is urgently needed on the results to be expected from their trial in suitable cases This monograph, which has been brought well up to date, is an authoritative account based not only upon reports but on wide personal experience of the surgery of the sympathetic system

The great Sir William Turner, asked by a student where the sympathetic system begins, is reported to have roared "The sympathetic, Sir, has no beginning" There are even now wide gaps in our knowledge of the anatomy and physiology of the system, but a useful summary of current ideas is supplied in the first chapter of this book, due weight being given to the evidence in favour of a head end in the hypothalamic region The task of revision has apparently fallen to the junior author, since the preface to this edition is signed by his initials, and his skill in incorporating all the important new work without increasing the size of the monograph by more than a few pages merits warm praise Salient additions include sections on the clinical grading and prognosis of Raynaud's disease, on the recognition of localised structural disease of the main arteries, on controversial questions connected with afferent pathways in the sympathetic system, and on sympathectomy for dysphagia and associated conditions The work will assuredly continue to help active surgeons, and to guide younger men training for surgical appointments and for higher qualifications

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[1] See *Lancet* Sept 18th 1937, p 698

THE LANCET

LONDON SATURDAY OCTOBER 2 1937

ANOTHER NURSING INQUIRY

THERE is now a serious shortage of nurses, both of candidates for training and of applicants for staff posts, evidence is conclusive that this shortage is no longer local but general. Even those training schools whose prestige still maintains their waiting lists admit that advance bookings are greatly diminished and the news that an important hospital is having to close a ward for no other reason than inability to staff it has released many other institutions from the tension of trying to conceal their own position. The peculiar difficulty in which they are placed is that their very efforts to attract more probationers tend to increase the numbers required and also the demand for staff nurses This applies especially to the introduction of shorter hours and to the adjustment of the proportion of trained to untrained nurses so as to remove the reproach that probationers are overwhelmed with routine work and are not being systematically taught under supervision how to tend the sick.

We need not recapitulate the reasons for the present acute shortage but the fact is worth recalling that it was foreseen and might have been forestalled had not the temporary improvement in recruitment which coincided with the general slump given a false sense of security to those controlling conditions of service It is more than five years since the issue of the final report of THE LANCET Commission on Nursing[1] Between the inception of this commission and the conclusion of its task in January, 1932 a general decline in national prosperity had begun, and at the time of going to press the commission noted that recruits were coming in better in certain areas, an improvement attributed by some to the manifest advantages of a resident post in times of economic pressure The report of the commission created widespread interest, much praise and a measure of criticism which was mainly concentrated not on the accuracy of the data or of the deductions from them but on recommendations made—among more than 50 others—for the division of the preliminary State examination into two parts, of which the first (in anatomy, physiology, and hygiene) would be taken before the nurse enters the wards This proposal which was, and still is strongly supported by a progressive section of the nursing profession was designed partly to fill the gap between the ages of 16 when the prospective nurse often leaves school and 18 or 19 when she is admitted to hospital but it was intended also to lighten the burden on the probationer during her first year It was perhaps unfortunate that to this proposal was added a suggestion for the exemption from the relevant part of this preliminary examination of those who hold a university degree in one of the subjects, for this gave colour to the bogy that the division of the examination would endanger the one portal system of entry to the profession, which is rightly upheld as a vital part of its present organisation. Those nurses who have not ceased to advocate this change have already been encouraged by the fact that the General Nursing Council for Scotland has adopted it and will be gratified by the sympathetic reference to this vexed question made by the Minister of Health when he announced last week his decision to appoint jointly with the President of the Board of Education, a committee to make a comprehensive inquiry into the whole subject of the recruitment and training of nurses for the sick.

There has been no lack of constructive suggestion among the recent contributions to the lay press on the nursing problem, especially on means of bridging the gap between leaving school and entering hospital. An attempt has been made by the Surrey County Council to organise a special two years course for prospective nurses in one of their secondary schools this met with a poor response in the absence of bursaries or maintenance allowances The Middlesex County Council have been more successful with a somewhat similar course at the Kilburn Polytechnic A far reaching scheme for a national college to be subsidised by the State has been put forward by the secretary of the Queen Mary s Hospital for the East End Stratford and the alteration of the whole basis of training 'so that from first to last nurses shall be regarded and treated as scientific students whose education and instruction must take precedence over any other *considerations* is proposed by DR HAROLD BALME[2] We disagree with DR BALME (p 41) that such an alteration would be a logical outcome of the criticisms made by THE LANCET Commission their efforts were expressly directed to the adjustment to modern needs of the system of apprenticeship which they desired to retain not out of loyalty to tradition, but because they recognised that practical work in the wards is far the most important part of a nurse's training

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[1] Appointed in December 1930 "to inquire into the reasons for the shortage of candidates trained and untrained, for nursing the sick in general and special hospitals throughout the country and to offer suggestions for making the service more attractive to women suitable for this necessary work The members of the Commission were The Earl of CRAWFORD and BALCARRES, P C, K T, F R.S. (chairman) Miss M D BROCK, O B E., M.A. Litt.D headmistress, the Mary Datchelor Girls School. Miss L. CLARK, M B E., R.R.C., matron, Whipps Cross Hospital. Prof HENRY CLAY M.A., D.Sc. late professor of social economics in the University of Manchester Miss R E. DARBYSHIRE, R.R C matron, University College Hospital. Prof. F R. FRASER, M D F R.C.P., professor of medicine in the University of London physician to St. Bartholomew s Hospital. Mr A. LISTER HARRISON J P., chairman committee of management Metropolitan Hospital. Dr ROBERT HUTCHISON F.R.C P., physician to the London Hospital and to the Hospital for Sick Children, Great Ormond-street. Mrs. OLIVER STRACHEY, chairman, employment committee, London and National Society for Women s Service. Miss EDITH THOMPSON, O.B E., member of council Bedford College, University of London. Sir SQUIRE SPRIGGE, M D., F R.C.P., editor of THE LANCET with Dr M. H KETTLE, an assistant editor as honorary secretary The Final Report of the Commission was issued in February, 1932 and is obtainable from this office (7 Adam street Adelphi W C.2) for *2s 6d.*

[2] A Criticism *of* Nursing Education with suggestions for Constructive Reform By Harold Balme M.D Durh. F R.C.S. Eng D.P H Lond. London, Humphrey Milford Oxford University Press 1937 Pp 80 *2s. 6d*

Concentration on practical nursing duties for long periods without the distraction of attendance at lectures or classes is indeed a feature of the most up to date method of training—the "block" system which has been tried with success in Warsaw and in some Scandinavian hospitals and has just been adopted at University College Hospital At various stages of their course the probationers go back to the training school for a few weeks during which they divide their time between lectures, classes, and private study, doing no hospital work at all This alternation between periods of instruction and periods of physical activity seems to work well in preserving a fresh outlook and preventing fatigue, but it cannot be instituted unless much more sleeping accommodation is available than will house the complement of nurses needed for the routine work of a hospital Among other recent proposals for the reorganisation of the nurse's work or training there remains to record a draft charter prepared by the Trades Union Council who would like to enforce improvement in the conditions of service offered to nurses by organising the profession on trades union lines, with a Whitley Council to act as a supervising and coördinating body to determine minimum rates of salary and maximum hours of duty It is safe to predict that this movement will not prosper among nurses It is rather in an understanding between the healing professions and educational and hospital authorities that hope lies Doctors especially can no longer stand aloof and ignore the failure to recruit enough nurses to keep pace with the demand, for patients are beginning to suffer The British Medical Association made a good start last year by appointing a committee which considered various points raised by the College of Nursing and endorsed the appeal to the Ministry of Health to lend a hand But even since this committee made their report this summer, the situation has changed for the worse

The only new cause suggested[2] for the present shortage is the declining birth-rate, and the suggestion is worth examining if only because it is a fresh one, most of the other "causes" being only too well established, in the words of a contemporary, we are willing to do everything about them except change them If the birth rate is a considerable factor in the present shortage there is likely to be another deceptive respite, for it will hardly operate next year, or for a year or two after, only to act with alarming and increasing force in the years after 1940 Girls now 20, 19, and 18 years old were born in 1917–19, and in those three years the total number of female live births in England and Wales was exceptionally low—viz, 986,731 against 1,292,669 in the three years 1911–13, and 1,214,704 in 1914–16 Expressed as rough annual averages, in thousands, these figures represent 329 per annum in 1917–19, 431 in 1911–13, and 405 in 1914–16 The war slump may therefore be relevant to the shortage of candidates, but it must be remembered that this slump was followed by a bumper year and that in 1920 there was registered the largest number of births ever recorded in a year, including 466,812 female live births These children are now 17 and should provide a relatively large source of supply in 1938 and 1939 But in the more remote future recruitment of nurses may be gravely affected by the diminishing birth rate In 1924–26 the female live births numbered 1,044,424, in 1927–29, 958,551, in 1930–32, 925,512, and in 1933–35, 865,656, or, as rough annual averages, in thousands, 348 in 1924–26, 320 in 1927–29, 309 in 1930–32, and 290 in 1933–35 In a 10 year period the number of female live births has fallen by nearly 60,000 per annum Reduction in mortality can do little to increase the subsequent population at adolescent ages Presuming no mortality (or migration) whatever, the number of girls reaching their 17th, 18th, and 19th birthdays in 1940 will be 1,165,419, in 1950 the corresponding number would be 891,765, or nearly a quarter of a million less With a concurrently increasing number of old persons, needing probably a higher ratio of nurses to population, the outlook is not encouraging The more reason therefore not only to take official cognisance of the other causes of the scarcity of nurses but to take immediate action to mitigate them

VACCINATION AGAINST YELLOW FEVER

SOME regard yellow fever as the most important problem in epidemiology for the world to day Having selected it as a disease pre eminently preventable, the Rockefeller Foundation formed a commission twenty years ago for its complete eradication, and, in the words of A W SELLARDS, who has been a pioneer in this territory, "some of the members could hardly wait to begin work for fear the disease would just vanish before they could make a start"[1] By 1925 it did indeed seem that yellow fever was on the point of extinction in the New World, and the attack was to be transferred to Africa But since then the recognition of "jungle" or "silvatic" yellow fever in Brazil by SOPER and his colleagues, the discovery by means of the mouse protection test of "silent" areas in Africa and South America, the recognition that certain species of monkeys may serve as reservoirs for the virus, and last but not least the development of air transport capable of bringing infected passengers and mosquitoes to lands hitherto immune—all these have profoundly altered the situation

By way of encouragement, on the other hand, we have gained a new ally, for the future, in vaccination Though lusty, this ally is still but an infant, and as to its upbringing there are two schools of thought All have agreed of late years in using living virus, for the first attempts with killed virus were largely ineffective, but after MAX THEILER's demonstration in 1930 that viscerotropic virus, rendered neurotropic by passage through mice, loses its virulence but still confers immunity, two different series of vaccinations were begun—in America by SAWYER, KITCHEN, and LLOYD, and in Africa by SELLARDS and **Laigret**. In both series neurotropic mouse virus was used at first, but in the United States it was made less potent by adding human (and later monkey) immune serum, whereas in Africa it was given alone after attenuation by storage in glycerin. Subsequently **Lloyd**, **Theiler** and **Ricci** used viscerotropic monkey virus attenuated by culture for two years on embryonic tissue, still with the addition of immune serum; but the latest development is immunisation with attenuated pantropic virus alone, and by May last G. M. **Findlay** had immunised 65 persons by this means without ill effects.[2] The time has not yet come for judging between the two agents—neurotropic mouse virus on the one hand and pantropic monkey virus (with or without immune serum) on the other—particularly since the methods of using both are continually being altered and improved. Two serious objections however are raised against the use of neurotropic mouse virus. The first is that it circulates in the blood for some days after inoculation, so that it is theoretically possible for yellow fever to be spread by inoculated persons if they are bitten by the mosquito vector. **Stefanopoulo** has managed to infect monkeys in this way, though with some difficulty, but in practice no case of infection derived from vaccinated persons has been known in French West Africa and the risk is generally considered very slight. Secondly there is the possibility of a neurotropic virus causing nervous lesions in the person who is inoculated with it. This has happened fairly often —indeed in 3 or 4 out of every 1000 inoculations. This incidence is greater than the incidence of similar complications after vaccination against rabies or small pox, but in estimating its importance it must be remembered that at least one case has been recorded[3] of encephalitis following serum virus vaccination, though this has been performed far less commonly than neurotropic virus vaccination—perhaps on 1500 persons compared with more than 20 000. Nevertheless the balance of opinion at present seems to favour the American method as carried out by **Findlay** in this country and **Pettit** and **Stefanopoulo** in France rather than the neurotropic mouse-virus vaccination associated particularly with the names of **Sellards** and **Laigret**. At least the yellow fever commission of the Office International d'Hygiène publique last year held it advisable to exercise the greatest care in vaccination with neurotropic mouse virus, especially if used without the addition of immune serum. They added that though vaccination should be recommended to all persons exposed to the risk of yellow fever, the time was not yet ripe for preventive vaccination en masse.[4]

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[2] *Med Offr* July 24th 1937 p 36

[1] Sellards A. W, *New England J Med* 1937, 216 455

Laigret claims that about 20 000 persons have been vaccinated in Africa during the last three years and that none of them have afterwards developed yellow fever. On the other hand a serological estimation of the immune titres of 19 persons inoculated between one and two years previously showed that in 4 the protective properties of the blood had disappeared.[5] After a natural attack of yellow fever immunity sometimes lasts a lifetime, but **Laigret** estimates that the protection given by his virus vaccine will not last more than five years, even under the best possible conditions, and he advises revaccination every two years or more often in face of epidemics. Serum virus vaccination probably confers an immunity of about the same duration, although comparison is said to have revealed lower immune titres than in those vaccinated with neurotropic mouse virus alone.

BETTER FO'C'SLES

The recent issue by the Board of Trade of revised Instructions as to the Survey of Masters and Crew Spaces aims at securing improved conditions for those manning vessels of the British mercantile marine. It has a particular importance for port sanitary authorities throughout the country in their endeavour to obtain and maintain satisfactory hygienic standards in crew quarters. The importance of the hygiene of crew spaces as a subject requiring the attention of public health authorities was first emphasised by **William Collingridge** in a paper read in 1894 before the Shipmasters Society and published in our own columns. Within recent years the medical officers of several ports, including London, Liverpool, Manchester, Southampton and Hull, have dealt in detail in their annual reports[6] with the nature of the accommodation provided for ships' crews. They are in agreement that conditions in many fo'c'sles are unsatisfactory, and that the *general* standard of accommodation found in British vessels is inferior to that characteristic of ships of Scandinavian, German and certain other nationalities. Criticisms voiced by marine hygienists of conditions in crew quarters have not been purely destructive. **Collingridge**'s paper was notable for the recommendations it contained, and at intervals since its appearance constructive proposals similar in nature but modified to meet modern requirements have been made by such authorities as Dr. J. **Howard-Jones**,[7] the late Fleet-Surgeon **Home**[8] and Dr. **Greenwood Wilson**,[9] while suggestions regarding crew spaces in merchant ships were published in 1931 and 1935 by the Association of Port Sanitary Authorities of the British Isles. The seamen and firemen of the merchant service have also pressed for better quarters, and their trades unions were partly responsible for the superiority of accommodation in standard vessels built during the late war. In 1930 recommendations directed towards the improvement of crew spaces were issued by the Shipping Federation, and they were revised in 1935. Although resembling those of the Association of Port Sanitary Authorities they were less comprehensive. In practice their application was limited, but most of the proposals of the Federation were adopted for vessels constructed according to plans approved by the Board of Trade under the "Scrap and Build" scheme.

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[2] Communication to the Committee of the Office International d'Hygiène publique May 1937.

[3] Sawyer, W. A., Amer. J. Hyg. 1937, 25, 721.

[4] Bull. Off. int. Hyg. publ. 1936, 28, 1301.

[5] *Bull. Soc. Path. exot.* 1937, 30, 8.

[6] White, C. F., Ann. Rep. Port of London Health Authority 1935; Fraser, W. M., Ann. Reps. Liverpool Port Sanitary Authority, 1935 and 1936; Dearden, W. F., Ann. Reps. Manchester P.S.A., 1928, 1936; Williams, M., Ann. Rep. Southampton P.S.A. 1936; Gebbie, N., Ann. Rep. Hull and Goole P.S.A. 1936.

[7] Howard Jones, J., *J. R. sanit. Inst.* 1915, 36; *Lancet*, 1913, 2, 887.

[8] Home, W. E., *Proc. R. Soc. Med.* 1926, 19, 95; *Lancet*, 1930, 1, 423.

[9] Wilson, J. G., *Lancet*, 1935, 2, 645.

In the past few months a joint committee of the Board of Trade and the Ministry of Health has been revising the old Instructions, in consultation with the interests concerned, and the new Instructions are the result of their deliberations. They are already in force, and in the case of new tonnage have made legal requirements of many of the improvements advocated for a number of years by port medical officers and the Association of Port Sanitary Authorities. They provide for healthier and more congenial quarters by requiring that accommodation be placed amidships or aft, and that watches have separate sleeping spaces, and by ensuring more satisfactory ventilation and lighting. They facilitate personal hygiene and general cleanliness by requiring the provision of improved washing facilities, lockers suited to the storage of clothes, and spaces reserved for drying clothes and for hanging oilskins. The welfare of crews receives further attention in the instruction that the crew accommodation in vessels sailing to the tropics shall be fitted with adequate mosquito protection, and that there shall be a hospital in all ships of 2500 tons gross or over. The 1937 Instructions differ from those previously in force in that they neither encourage nor permit of a wide interpretation of their requirements, and improvement will undoubtedly follow their application. It is to be noted, however, that not all the reforms advocated by the Association of Port Sanitary Authorities have been adopted. The provision of a messroom near the galley and the supply of hot fresh water in washrooms are not insisted upon, and the benefits to the crew of including a messroom boy among their number are not emphasised. These useful items of further progress must not be forgotten.

The *provision and maintenance of hygienic* conditions in crew spaces raise peculiar difficulties. The revised Instructions represent a serious attempt to grapple with these difficulties, but it is not to be expected that they will solve all individual problems arising in vessels of special types or engaged in particular trades. For the revised Instructions to achieve complete success it will be necessary to enlist the sympathetic coöperation of shipowners, shipbuilders, and sailors. There is evidence that this cooperation will be forthcoming. It will be tested most severely by the problems presented by existing ships. The Instructions are not retrospective. Although they point out the need for improving accommodation in old vessels, it is important that sight should not be lost of the fact that the standard of accommodation now required in new ships is that considered by sanitarians to be the minimum essential for the health and welfare of crews. Our shipyards are capable of providing accommodation second to none. It rests with the owners to insist on its provision, with masters to supervise its maintenance, and with the crews to make of it their home while at sea.

CHEMOTHERAPY FOR VIRUS INFECTIONS?

AN investigation of the way in which sulphanilamide affects the multiplication of hæmolytic streptococci is described by a group of Sheffield workers on p. 792, and it is interesting to find them recording, inter alia, that the drug may at first actually stimulate the growth of streptococci in the blood. This stimulation is followed by depression, and they discuss the action of the remedy in the light of their observations that sulphanilamide is relatively soluble in the fatty envelope of the cocci and that (in the rabbit) it seems to increase the phagocytic activity of reticulo endothelial cells and the production of polymorphs by the bone marrow. The number and variety of organisms that are said to be attacked by sulphanilamide and more or less related drugs is so great that it hardly comes as a surprise to find it stated that they are also active against a virus disease. Rosenthal and his colleagues[1] recall that Levaditi found Prontosil ineffective against herpes virus infection in rabbits and lymphogranuloma inguinale in a monkey, and in their own experiments with mice they have had no success with the virus of encephalitis (St Louis type) or of influenza. On the other hand they report that prontosil (4-sulphonamide 2 4′ diamino azobenzene) has a definite protective action, in large doses, against the virus of lymphocytic choriomeningitis, and this they believe to be the first instance of chemotherapeutic activity of a drug against a virus disease. It is noteworthy that prontosil soluble, as well as sulphanilamide and other related compounds not containing an azo linkage, proved inactive against the virus, though more potent against bacteria. It is hoped that this specialised activity of red prontosil may point to ways of making progress in the chemotherapy of viruses.

A GIFT of £80,000 has been made by Mr Harry Oakes to St George's Hospital, London. This sum, which is the largest single contribution yet made to the rebuilding fund, will enable work to be started on the new hospital next year. It was intended that the rebuilding should be done in three sections, but Mr Oakes's action has made it possible to proceed with the first half. The site to be covered includes all the ground as far as the old Underground station of Hyde Park Corner. St George's has long owned half the estate, and the other half was purchased from the Duke of Westminster in 1906, at a very low figure. The arrangement then made, however, was that this land would revert to the Westminster estate if the hospital moved elsewhere. Lord Willingdon, chairman of the rebuilding council, states that "no satisfactory offer for the property has ever materialised" and that no suitable alternative place for the hospital has been discovered. "To depart from the site is not only, therefore, economically unsound but impracticable." The new St George's will contain 520 beds instead of the present 330, and there will be 50 "private beds for persons of limited means."

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[1] Rosenthal, S M, Wooley, J G, and Bauer, H *Publ Hlth Rep Wash* Sept 3rd 1937, p 1211

ANNOTATIONS

LATENT SYPHILIS

In the present state of knowledge the most reliable sign of syphilitic infection is a positive serum reaction and to say that the infection is latent is simply to admit that its site of activity is for the moment unknown A positive reaction is often found more or less accidentally in the examination of blood donors at antenatal clinics or in the routine of hospital treatment, and in the absence of other signs it may be taken too lightly Cannon [1] describes 96 such latent cases seen in the last two years at the Vanderbilt Clinic in New York or in private practice in which the symptoms were not at first suspected either by patient or doctor of being syphilitic, but which yielded so readily to antisyphilitic treatment as to suggest that the disease was at least a contributory cause Once the idea of syphilis arose a number were found to show suggestive signs such as sluggish pupils absent knee jerks, an accentuated aortic second sound or a history of repeated miscarriages. Of this group 21 sought treatment for gastro intestinal disorders Vague dyspepsia and flatulence without definite relation to food was the commonest complaint but 3 patients had vomited blood, 2 had had melæna, and others complained of burning sensations in the abdomen or of pain in the right iliac fossa. Seven of these had been found to have cardiovascular disease which may have been the basis of their dyspepsia and various diagnoses had been attached to the rest after thorough investigation Antisyphilitic treatment cured or strikingly improved 16 of them when dietetic or other measures had had little effect A second group of 18 patients had respiratory or cardiovascular symptoms usually of long standing such as cough pleuritic pain, asthma, sore-throat, hoarseness or sinus trouble and their diagnoses had ranged from a common cold to pulmonary tuberculosis Many were referred from the tuberculosis clinic to which their cough with expectoration night sweats loss of appetite and weight and pains in the chest had naturally led them but where no confirmatory signs of tubercle had been found. A group of 9 patients complained of urinary troubles—frequent difficult, or painful micturition, slight enuresis acute retention, hæmaturia, or pain in the lower part of the back. Several of these gave a history of gonorrhœa but had not been relieved by suitable treatment and all but one responded to syphilitic remedies by lessening or disappearance of symptoms A number of women with menorrhagia or metrorrhagia were cured by antisyphilitic treatment while awaiting admission for operation The remainder of the 96 patients were sent to the clinic for conditions as various as vague mental or physical ill health, thyroid enlargement subcutaneous swellings painful mandibular joints glycosuria and inguinal hernia

In Cannon's experience if there is no active syphilitic process of the brain structure all asymptomatic patients can be made Wassermann negative if the best drugs are used and if the treatment is continuous and persisted in long enough and he recommends the thorough treatment of all who show a strongly positive Wassermann reaction even in the absence of other signs He does not claim that all of his 96 patients were suffering solely from syphilis; some for instance probably had an associated tuberculosis; but he does make out a strong case for routine serum tests for careful inquiry for a syphilitic history and for examination of the nervous system heart and aorta and eyes wherever an ailment proves obscure or obstinate

CINERADIOTHERAPY

Under this name Prof A. O Almeida describes a new technique of X ray therapy in which the beam of rays instead of being centred at one point on the skin is moved regularly over a given area. The tube is mounted in a carriage drawn from side to side at a constant speed by an electric motor working through gears and is itself moved up and down within this carriage by another similar mechanism The area over which the tube will operate, and the speed of movement of the beam relative to the field of irradiation can be precisely regulated. Prof. de Almeida and his colleagues claim that by this means the distribution of the dose and its decrease in accordance with the depth of the tissues and the distance from the centre of the beam may be modified at will so as to make it as homogeneous as possible over the whole of the irradiated tissues or to concentrate it on any given point within them. He argues that, as the dose is the product of intensity and time the time factor is the one to vary in order to control the dose administered to a given volume of the body His experiments have reached the stage of depth dose determination with wax phantoms and he claims to have obtained percentage depth doses of 93 1 per cent at 40 cm and 87 7 per cent at 90 cm These figures, as his assistants point out in their report, are far in excess of those obtainable with a fixed tube. The mathematical basis of the results is worked out fully in the same number of these proceedings, which are published in English as well as Portuguese. Radiologists will await with interest the clinical results of moving tube treatment. The principle could obviously be applied to therapy by a radium bomb

A NEW SPECIFIC FOR AMŒBIC DYSENTERY

The seeds of ya tan tzu a plant well known in South China Malaya, and India, have been used since 1765 in the treatment of diarrhœa, hæmorrhoids and chronic dysentery It is known botanically as *Brucea sumatrana* and its properties have been investigated for more than a year by Dr Liu Hsiao Liang [2] of Chefoo Shantung An alkaloid brucamarine has been separated from the seeds and Physalis and Bertrand have found a bitter glucoside they call kosamine. Dr Hsiao Liang has treated 19 patients suffering from acute or chronic amœbic dysentery with this preparation and 80 per cent. have been benefited These cases were diagnosed by demonstrating the active parasite in the stools; no other amœbicidal drug except ya tan tzu was given. The dose was determined by a study of the Chinese literature and also from animal tests. To adults 20–50 seeds—unbroken but with the shells removed—were administered in capsules in a single dose, or in several divided throughout the day The amœbæ disappeared from the stools in 2 cases in a day in 7 cases after two days, in 4 after three days, in 1 case after five days and in another after six days.

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[1] Cannon A B., *J Amer med Ass.* 1937 109 318

[1] *Archivos da Fundação Gaffrée e Guinle*, Rio de Janeiro June 1937

Because of the great relief derived from this treatment, it was difficult to follow up the after history of these cases, but it is known that 6 relapsed The dysentery in these latter patients responded to further treatment and 2 of them reported no further trouble after two months One patient passed six dead ascarides after taking the powdered seeds—oil free after ether extraction. Toxic symptoms produced by the seeds were nausea, vomiting, abdominal pain, and purging, but these were never severe The main advantages claimed for this form of treatment are that the remedy is obtainable from any Chinese drug store, it is easily prepared and can be administered by the mouth.

RADIODERMATITIS AND CANCER

THE X ray cancer of the skin never appears de novo A radiodermatitis, usually of long duration (3–20 years), always precedes it, and this too may not develop until months after the last exposure to the rays Thus Simone Laborde [1] reports the case of a woman who was treated with repeated doses of X rays in 1910 for hypertrichosis

> The result was perfect at the time and it was not till three or four years later that the characteristic atrophy with pigmentation and telangiectases appeared on the chin and on the mucocutaneous borders of the lips Some ten years later, in 1924, she applied for treatment of a small ulcer that had appeared on the edge of the upper lip Histologically it was a squamous carcinoma, and a dose of X rays previously applied at another clinic had had no effect on its evolution It yielded promptly to the gamma rays of radium, and remained healed for three years, but further treatment for recurrences was required in 1928 and 1934

This history is typical and many another example could be found wherever X rays are used either for diagnosis or treatment If such happenings are to be avoided—as assuredly they can be—every radiotherapist must acquaint himself and his assistants with the factors of causation as clinically observed and experimentally proved Laborde summarises them under four headings (1) The individual X ray dose that causes dermatitis is always small lightly filtered, and repeated at varying intervals over a period of months The hard penetrating gamma radiation does not produce cancer, on the contrary it is used in its treatment The softer, less penetrating, radiations have their carcinogenic analogue in the rays of the sun in Australia, where cancer supervening on chronic solar dermatitis is a commonplace (2) There is always a latent period before malignant proliferation begins It varies very widely, but its average length is 5–10 years during which there is always a more or less demonstrable dermatitis This is to be regarded as a true pre cancerous stage, closely resembling leukoplakia of the tongue (3) The great majority of X ray cancers are squamous celled, but X ray sarcoma can also occur, particularly in relation to bony epiphyses and where there has been previous tuberculous infection such as lupus verrucosus Hellner [2] reports that he has induced such sarcomas in the bone marrow of rabbits by repeated application of radium, and he recalls Schurch and Uehlinger's similar results with mesothorium paste implanted in bony cavities (4) Of the greatest importance from the physiotherapeutic point of view is the relation which these X ray cancers bear to their environment It is accepted that once cartilage or bone has been invaded the hope of a cure with X rays or radium is small The cancer cells have become radio resistant in a physical sense, because they are protected by the calcium deposits around them Besides the physical, however, there is the more complex biological problem Why is it that some malignant growths (e g, rodent ulcer or sarcoma) are more radio-sensitive than others (e g, squamous celled)? The question seems no easier to answer now that we recognise that soft rays encourage malignant growth while hard ones counteract it And finally, we have to reckon with biological reactions that have been modified, maybe, by long standing dermatitis Here there must be profound alterations in the functions of the basal or germ cell layer of the epidermis, such as are clinically demonstrated by characteristic shifting of pigment and the appearance of small warty excrescences Endarteritis and destruction of elastic and connective tissue are always to be seen in microscopical sections, and dye staining shows how extensive is the biochemical dysfunction that the ailing and atrophic tissues as a whole are undergoing In the words of Laborde, "la radiosensibilité des cancers dépend à la fois de l'action du rayonnement sur les cellules néoplasiques et sur le milieu dans lequel elles se développent"

A R P

THESE sinister initials are being made more and more familiar by a spate of books on air raid precautions, designed to instruct either the profession or the public To the five handbooks already issued by the Home Office, a new one, of greater value to medical men, has now been added on the medical treatment of gas casualties [1] Apart from the "Manual of Treatment of Gas Casualties," published in 1930, this is the only standard work on the subject Though small it is comprehensive, and it deals thoroughly with the gases thought likely to be used in war, their effects, the differential diagnosis and treatment Those who find this new knowledge hard to memorise may be glad of a brief booklet [2] by Dr J Fenton, deputy medical officer of health of Eastbourne, who summarises first aid measures against gas, particularly for the information of St John Ambulance workers Dr Haden Guest,[3] besides dealing with gas casualties, covers other aspects of air raid precautions, and describes means of protecting the home, industry, and vital services, the organisation for doctors, first aid, and hospitals, and such measures as decontamination Commending the book in a preface Lord Dawson says that "the author makes it clear that air warfare creates a new situation in that it may directly attack the civil population It becomes necessary, therefore, that men and women should know the nature of the risks to which they would be exposed and how to protect themselves therefrom" The fourth book under review is a much more elaborate work, on the air defence of the civil population, by a barrister and an engineer [4] Of limited medical interest, it is a grim exposé of the past history and present state of air attacks on the civil population and of how these attacks are being prepared for chapters are included on individual and collective protection structural precautions and the measures taken in foreign countries The conclusion forced upon the reader of these various books as of our daily news papers is that applied morals must somehow be made to keep pace with applied science.

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[1] Laborde S *Rev Physiothér* 1937 13 89
[2] Hellner H *Münch med Wschr* 1937 84 980

[1] Air Raid Precautions Handbook No 3 Medical Treatment of Gas Casualties H.M Stationery Office 1937 Pp 145 6d

[2] Gas A Synopsis of Defence Against By John Fenton M B B Ch B A O D P H Deputy Medical Officer of Health, County Borough of Eastbourne County Surgeon St John Ambulance Brigade London Dale Reynolds 1937 Pp 52 1s

[3] If Air War Comes A Guide to Air Raid Precautions and Anti gas Treatment By Dr L Haden Guest M.C formerly Medical Instructor, Air Raid Precautions Department Home Office London Eyre and Spottiswoode 1937 Pp 88 1s

[4] Air Defence and the Civil Population By H Montgomery Hyde M.A D Lit, and G R. Falkiner Nuttall M.A London Cresset Press 1937 Pp 230 12s 6d

DEVELOPMENTS AT HARROGATE

On Oct 6th Sir Kingsley Wood will lay the foundation-stone of a new extension of the Harrogate Royal Baths The improvements now to be made have been under consideration by the corporation for several years and great pains have been taken over design and equipment Two years ago a committee of officials and members of the Harrogate corporation visited spas both at home and abroad and the new block of buildings will incorporate interesting new developments and devices in balneological treatment The extension includes (1) an entirely new block of buildings adjoining and connecting the present baths (2) reconstruction of the winter gardens and (3) general refitting of the existing bathing establishment at the Royal Baths It is expected that the developments will be complete in about two and a half years The estimated cost is £66 000

B C G

Dr Birkhaug[1] writes with unusual detachment about B C G At the invitation of Prof Calmette he spent several years in Paris studying tuberculosis at the Pasteur Institute and now as a member of the staff of the Christian Michelsen Institute in Bergen, he is entrusted with the task of preparing B C G cultures for administration in Norway His survey will give complete satisfaction to neither of the two parties that have waged such spirited war on each other over B C G and just because he is neither hot nor cold he will prove exasperating to the gladiatorially minded. A pendant to his opinion that B C G is no *virus fixe* is that there are good grounds for believing that on further culture it will ultimately lose its present power of immunising against tuberculosis His examination of the conditions under which the gospel of B C G has been preached in certain quarters reveals not only an ignorance of elementary rules to which statisticians should submit their calculations but an irascibility that is inappropriate to scientific debate His own view nevertheless is favourable since he holds (1) that B C G never provokes progressive and fatal tuberculous lesions even in the most receptive subjects ; and (2) that it is pre-eminent among tuberculosis vaccines in its capacity to enhance resistance to the infection—notably when it is given by intracutaneous injection rather than by mouth.

MONGE S DISEASE

Very little is heard in England about the disease of great altitudes first fully described by Monge in 1928 which is in America, usually called by his name On this side of the Atlantic our attitude towards altitude is perhaps, more academic and less clinical but Monge s descriptions of symptoms are of value to the physician whose work brings him into direct contact with patients rather than experimental animals In the paper under review[2] he does not deal with the symptoms of acute mountain sickness but is concerned rather with the occasional failures to acquire the necessary adjustments for life at great altitudes and with the loss of these adjustments once acquired His subacute mountain sickness which corresponds essentially to the disease of mountaineers described by the doctors attached to the various Himalayan expeditions may progress to a severe form of altitude erythræmia, called by him chronic mountain sickness Here he overlaps the earlier work of Barcroft but his observations are wider and cover every system of the body He describes the cyanotic appearance of those whose adaptation has failed the congestion of the mucous membranes clubbed fingers emphysematous thorax, dyspnœa lassitude blurred vision mental changes and nausea but does not mention that much of the digestive disturbance is now known to be due to a slowing in the emptying time of the stomach He also omits all reference to Campbell s work on the liver but his account is admittedly condensed

In many of its essential signs and symptoms Monge s disease is very like the essential erythræmia of Vaquez It differs from it chiefly in the immediate relief obtained by a descent to sea level

SURGEONS FROM BARBERS

An invitation to deliver the Thomas Vicary lecture at the Royal College of Surgeons of England was the origin of an entertaining monograph now published by a distinguished physician[1] Dr Wall s subject developed as he studied it and he quickly perceived that the compass of an hour s lecture was wholly insufficient to do justice to the story which he now presents in detail The separation of the two component parts of the Barber Surgeons Company was determined by a laudable aspiration on the part of the surgeons to raise the status of their profession ; and though the barbers were opposed to the proposal a committee of the House of Commons came to the conclusion that the surgeons had made out a good case and that the creation of a separate Company of Surgeons would contribute much to the improvement of surgery and thereby become a matter of public utility In 1745 therefore the surgeons company was incorporated as a company on similar lines to other city companies with a master wardens court of assistants liverymen and, since the surgeons were the official examining body for the medical entries to the Navy the Army and the East India Company's service a court of examiners The new company emerged from its old association with the barbers with little material endowment all the real and personal estate except the Arris and Gale trust funds remaining with the barbers It started under the handicap of being without a meeting place or even a headquarters negotiations for the use of their old rooms at the Barbers Hall proving impracticable The story presented by Dr Wall suggests that the barbers were resolved to have no further dealings with their former associates and were certainly not inclined to help them However another city company the stationers came to the rescue apparently for a monetary consideration The company having thus provided for the immediate needs of the examinations and dissections proceeded to build its own hall which was situated on the eastern side of Old Bailey Originally it had been visualised as becoming a centre of surgical education but this aspiration remained unfulfilled and for the whole period of its existence it remained purely an examination hall and livery hall, with a residence for the company's clerk Forty years later Gunning told the court " Your theatre is without lectures, your library without books your committee room become your clerk's eating parlour " The company, however, survived some awkward financial embarrassments and became steadily more prosperous, until in 1797 it removed to a new site in Lincoln's Inn fields, and after many vicissitudes and much opposition both in and outside Parliament was dissolved and converted by charter into the Royal College of Surgeons of England The story of the struggles that preceded the charter, if somewhat involved, is absorbingly scandalous , it seems that the company, or rather the court of examiners, which had arrogated to itself the real power, had in a variety of ways trespassed against the law, and that the proceeding by charter was a means of extricating itself from its legal embarrassments The history of the surgeons' company, though it covered but a short period of surgical history, is curiously illuminative of the life and manners of the eighteenth century Sir D'Arcy Power, in his foreword, says " The result of Dr Wall's work has been to show that London surgeons have remained true to type, excellent craftsmen, but shockingly bad at business " The twentieth-century surgeon who has had to submit to criticism of an opposite order may feel gratified by this verdict

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[1] Birkhaug K Nord med Tidskr August 14th 1937 p 1333
[2] Monge C Arch intern. Med. 1937 59 32

[1] The History of the Surgeons Company 1745–1800 By Cecil Wall M.A. D M F R C P Thomas Vicary Lecturer at the Royal College of Surgeons of England 1935 London: Hutchinson s Scientific and Technical Publications 1937 Pp 356 10s 6d

YELLOW HEADLIGHTS IN FOG

The question whether coloured headlights give greater visibility to the motorist at night and in foggy weather is answered in a report[1] issued on Thursday The answer is based on " the most reliable information known at the present time," and it is perfectly definite—namely, that none of the claims made in favour of using a coloured, and in particular a yellow headlight beam, rather than a white beam of no greater power, have been substantiated, and the claim for a greater range of visibility in fog may be regarded as definitely disproved On the possibility that a colour filter offers advantages by reducing dazzle the report reserves judgment, and the chairman of the Illumination Research Committee is careful to say that no account has been taken of the personal preferences of individual motorists

THE C S M M G

The Chartered Society of Massage and Medical Gymnastics—whose cumbrous name has become a source of distress to some of its loyal members—entertains at dinner every year at the Café Royal, Regent-street W , the medical men who contribute to its annual congress and a few fortunate others The evening's entertainment is always timed with discretion, the balance being well maintained between dinner, speeches, and dancing On Sept 22nd Dr J B Mennell presided, and Mr H A T Fairbank proposed the toast of the Society, calling attention to its growth in status and in numbers and to the tolerance shown by members to young doctors who prescribed treatment Miss G U Pratt in reply, referred to the projected research scholarships for members, and Miss J H Wicksteed, before proposing the guests, explained to Mr Fairbank that it was a poor masseuse who could not receive from a young doctor the instructions she wished to be given Sir William Willcox, in response, spoke, as past master of the Society of Apothecaries, of the value of the National Register of Medical Auxiliary Services, and drew attention to the expansion in recent years of the activities of members of the society who were as well qualified to guide the public in developing a healthy physique as to remedy postural or muscular defects Dr F A Roper, bringing greetings from the west country, said that propaganda was still needed to convert the medical profession as a whole to a proper appreciation of the importance of the Society's work, but that its best missionaries were members practising at the periphery, whose skill, loyalty, and judgment were beyond praise Dr W J O'Donovan, in a racy speech, proposed the chairman's health, the toast being received with great enthusiasm before the party moved away to dance

TENTH INTERNATIONAL CONFERENCE ON TUBERCULOSIS

Delegates from many nations attended the conference, postponed from last year, which was held at Lisbon early in September The main subjects for discussion were (1) the radiological aspects of the pulmonary hilum and their interpretation (with Prof Lopo de Carvalho as the chief rapporteur) , (2) primary tuberculous infection in the adolescent and adult (Dr Olaf Scheel, Norway) , (3) the open case of tuberculosis in relation to family and domestic associates, entrusted to Dr Charles J Hatfield (U S A) and Dr D A Powell (Great Britain), the latter unfortunately not being present to read his communication Many of the papers were good, the most original being that of Prof Lopo de Carvalho, whose radiograms demonstrating the intensified shadows at the hila by injection of sodium iodide through a probe impervious to Röntgen rays, and introduced through the median basilic vein, were remarkable These angiopneumographic experiments seem to have solved the problem of the interpretation of hilar shadows , in the majority of cases they are due to normal blood vessels As usual at these conferences the social arrangements were excellent , delegates thoroughly enjoyed the hospitality provided by the committee of the Union and by the Portuguese Government

The annual dinner and dance arranged by the London Panel Committee has this year been enlarged in scope so as to include every practitioner in the London area, their relatives and friends both medical and lay The dinner will take place at the Dorchester Hotel, Park lane, W , on Thursday, Oct 28th, at 7 30 P M The date was unfortunately misstated in an announcement in our last issue Tickets may be had from Dr A F Heald, 17, Russell square, W C 1

At 4 P M on St Luke's Day, Oct 18th, Sir Arthur Hurst will deliver the Harveian oration to the Royal College of Physicians of London His subject will be observation and experiment and the physiology of the stomach

Summer Time, which began in Great Britain, Ireland, the Channel Islands, and the Isle of Man on Sunday, April 18th, will end on Sunday next, Oct 3rd, at 3 A M , when the hands of timepieces should be put back to 2 A M. The hour 2–3 A M summer time will thus be followed by the hour 2–3 A.M Greenwich time

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[1] The Use of Coloured Light for Motor Car Headlights Department of Scientific and Industrial Research Illumination Research Technical Paper No 20 H M Stationery Office Pp 32 9d

SPECIAL ARTICLES

A COMPARISON BETWEEN THE OPEN- AND CLOSED CIRCUIT METHODS FOR DETERMINING THE BASAL METABOLISM

By J Douglas Robertson Ph.D M D St.And. D P H

CLINICAL CHEMICAL PATHOLOGIST TO THE MIDDLESEX HOSPITAL LONDON

(From the Courtauld Institute of Biochemistry Middlesex Hospital)

In the absence of the respiration calorimeter the most accurate of all instruments the method of choice in most laboratories for determining the heat output is by measuring the oxygen consumption.

There are two *methods in general use—the open* circuit and the closed circuit In the former some form of apparatus such as the Zuntz Goppert Tissot or Douglas bag is employed. The subject wears a face appliance with appropriate valves allowing him to breathe outdoor air while all the expired air over a certain period is collected and finally measured and analysed. In the latter some form of spirometer is used and into the circuit oxygen is introduced. The subject is attached to this apparatus—of which the Benedict-Roth, Benedict-Collins, Sandborn and McKesson *are types—by means of a mouthpiece* the nose being occluded by a clamp Valves or a motor blower direct the flow of air the expired air being lead through a chamber filled with soda lime to absorb the carbon dioxide and the amount of oxygen absorbed is calculated by noting the fall in the spirometer bell.

Theoretically the oxygen consumption measured by either of these methods should be equally accurate but Hunt (1926) found the closed-circuit method to give results 10–12 per cent higher than the open circuit His technique however seems open to criticism in that no control was done, showing that his subject s heat output was constant over the experimental period. It would be tempting to explain an increased oxygen absorption with the closed-circuit technique by postulating a solution of oxygen in the serum due to an increased pressure of this gas in the lungs and the stimulating effect of high concentrations of oxygen upon the metabolism; but neither in fact takes place Benedict and Higgins (1911) found as did Lavoisier and Seguin in 1789 that no increase in the *metabolism* took *place* by *breathing pure* oxygen. Zuntz (1903) and DuBois (1936) have shown that except in cases where there is a disturbance in the oxygen-carrying capacity *of the blood breathing oxygen* does not increase the amount of oxygen in the arterial blood

It was decided to re-investigate the accuracy and the relative advantages and disadvantages of the methods com*monly employed in* estimating the oxygen consumption

APPARATUS

Open-circuit method.—It was decided to use the Douglas *bag as this is most* commonly employed in this country. Its accuracy depends a great deal upon the gas analyses which are carried out in the apparatus *devised by* Haldane (1912) *but in addition* many check ups and calibrations were found to be necessary before results were accurate enough and comparable *It was found necessary to* —

1 Calibrate all the burettes in the Haldane gas-analysis apparatus. The difficulties of leaking at the rubber tube junctions were overcome by the *manufacture of* an all glass apparatus. The T bore taps were found unsatisfactory and they were replaced by two way diagonal bore taps of special construction. The Haldane apparatus was constructed by C Dixon and Co (27 Devonshire street London W C)

2. Calibrate the *spirometer* which measured the volume *of the* expired air *It was found that the spirometer* registered correctly only if the volume passing through it did not exceed 300 litres per hour

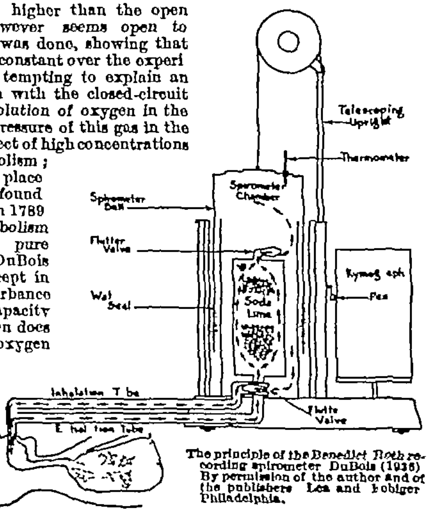
3 Analyse the gas samples in duplicate *on two different* Haldanes and in order to check the efficiency of the *apparatus an analysis of air* was done before and after the analyses on the specimens from the Douglas bag

4 Remove samples from the Douglas bag within 15 min of collecting the expired air in view of the ease with which carbon dioxide permeates the rubber lined bag

5 Test the Douglas bag for absence of leak.

Closed circuit method—I have used in this study mainly the Benedict Roth but also the British *Benedict (manufactured by H E Kendrick, 5 Lodge* Villas Woodford Green Essex) and a full description of the former machine is given by Roth (1932) The Benedict-Roth apparatus *with the entire closed* circuit is shown in the Figure

Flutter valves are used to direct the flow of air and they permit a *flow in one direction only A kymograph is* attached to record the movements of the spirometer bell and the drum is rotated by clockwork The drum is covered *with a paper* chart vertically ruled into accurately determined one minute spaces thus *no watches are necessary to record the time of an* experiment



The principle of the Benedict Roth recording spirometer DuBois (1936) By permission of the author and of the publishers Lea and Febiger Philadelphia.

The graphic way of measuring the oxygen consumption is of great importance and any *closed-circuit* apparatus that does not have a kymograph cannot be considered accurate The principle of the Benedict-Roth apparatus lies in its spirometer bell having a diameter of 16 24 *cm* By calculation it can be *shown that the area* of cross section of the spirometer bell is 207 3 sq cm Thus when the level of the spirometer bell falls 1 mm in an experiment it means that 20·73 c cm oxygen have been consumed and this at a respiratory *quotient* of 0 82 (the calorific value *of 1 litre of oxygen* is 4 825 calories) is equivalent to a production of 0 1 calorie If a 5-min.

reading is taken this would be equivalent to 1 calorie per hour. In an experiment, therefore, the fall of spirometer in 6 minutes when calculated in millimetres can be directly translated into calories of heat output per hour.

Before beginning the metabolism studies all apparatus was carefully calibrated by an alcohol check and details of the method have been published (Barrett and Robertson 1937). All machines were found to have a very high degree of accuracy with results varying from 99.5 per cent. to 101 per cent. of theory. All kymographs were timed with stop watches of known accuracy and it was found necessary to make some adjustments in three of them. It was found that carbon dioxide could be detected in the circulating air after passage through the soda lime when over 100 tests of ten minutes' duration had been done, so in practice the soda lime was changed after 80 tests to ensure purity of the air.

THE CONDITIONS

There are various factors that influence the metabolism of the body and the chief of these are food, digestion, work, rest, heat, cold, and fever. The standard conditions were those for so called "basal" or "standard" metabolism, by which the subject had fasted for twelve to fourteen hours.

THE SUBJECT

In comparing the two methods used in determining the oxygen consumption it is essential to determine that the oxygen consumption of the subject employed is constant over the experimental period. The observations were carried out on Miss A. A., who for the past seven years has attended this laboratory three times a week to allow me to measure her basal metabolism. Her heat output is constant over a period of at least 1½ hours, remaining in the region of 58 calories per hour.

TECHNIQUE OF EXPERIMENT

In order to avoid any upset that might be caused by changing mouth appliances when switching over from one method to another, it was decided to use the same mouthpiece and nose clip throughout, without removal during the whole experiment. The switch over from one apparatus to the other was done by arranging convenient tubing and valves; thus at the end of a reading on the Benedict Roth, the inhalation tube and exhalation tube were disconnected from the apparatus and into the former was inserted an inlet valve and into the latter an outlet valve. The exhalation tube was then connected to the Douglas bag. Miss A. A. had no knowledge when the change-over took place, nor was she aware of any change in sensation throughout the hour the whole experiment was performed. The sequence in which the types of apparatus were used was: (1) Douglas bag for 10 minutes; (2) Benedict-Roth for 10 minutes; (3) Douglas bag for 10 minutes; (4) Benedict Roth for 10 minutes.

RECORD OF EXPERIMENT

Barometer reading 752 mm.; room temperature, 22.5° C.; barometric factor = 0.893; calorific value of 1 litre of oxygen at a respiratory quotient of 0.82 = 4.825 calories. For the purposes of this comparison it was assumed that the respiratory quotient throughout was 0.82, but the significance and relative importance of this assumption will be discussed later.

First open-circuit experiment with Douglas bag.—

Volume of air expired in 10 minutes = 61.75 litres
Analysis of expired air { CO_2 = 2.71 %; O_2 = 17.49 %; N_2 = 79.80 %
Oxygen absorbed 21.14 — 17.49 = 3.65
R.Q. (respiratory quotient) $\frac{2.68}{3.65}$ = 0.74
By assuming R.Q. of 0.82 instead of 0.74 the number of calories per hour
$= 61.75 \times 0.893 \times \frac{3.65}{100} \times 6 \times 4.825$
= 58.3 calories

First closed-circuit experiment with Benedict Roth.—

Spirometer temperature { Beginning = 22° C; End = 22° C
Barometric factor = 0.895
Rise of oxygen line in six minutes = 64.5 mm.
With R.Q. 0.82 calorie output per hour = 64.5 × 0.895
= 57.5 calories

Second open-circuit experiment with Douglas bag.—

Volume of air expired in ten minutes = 66.4 litres
Analysis of expired air { CO = 2.77 %; O_2 = 17.70 %; N_2 = 79.03 %
Oxygen absorbed 21.07 — 17.70 = 3.37
R.Q. $\frac{2.74}{3.37}$ = 0.81
By assuming R.Q. of 0.82 instead of 0.81 the number of calories per hour
$= 66.4 \times 0.893 \times \frac{3.37}{100} \times 6 \times 4.825$
= 58.3 calories

Second closed circuit experiment with Benedict Roth.—

Spirometer temperature { Beginning = 22 C; End = 22 C
Barometric factor = 0.895
Rise of oxygen line in six minutes = 64 mm.
Assuming R.Q. 0.82 calorie output per hour = 64 × 0.805
= 57.2 calories

A comparison of the heat output of Miss A. A. by the different methods is given in Table I.

TABLE I.—*Heat Output*

Time (A.M.)	Method.	Heat output per hour (calories)
9.0–9.10	Douglas bag	58.3
9.13–9.23	Benedict Roth	57.7
9.25–9.35	Douglas bag	58.3
9.37–9.47	Benedict Roth.	57.2

DISCUSSION

A comparison of the open and closed circuits demonstrate that very close agreement is obtained. The relative advantages and disadvantages of these two methods of estimating the basal metabolism can now be conveniently summarised under the headings of (1) respiratory quotient; (2) the effect of breathing pure oxygen on the metabolism; (3) the accuracy of apparatus during the experiment; (4) the time involved in the calculation of the results.

Respiratory quotient.—It has been stated that the fundamental objection to the closed circuit method is the necessary assumption of a respiratory quotient, and the respiratory quotient usually chosen is 0.82 or the one of theoretical basal conditions. In the case of Miss A. A. the R.Q. of the first open circuit experiment was 0.74. By assuming the R.Q. was 0.82 the calorific value of a litre of oxygen was taken as 4.825 calories and the calculated heat output per hour was found to be 58.3 calories. On the other hand if the actual R.Q. of 0.74 had been employed the calorific value of a litre of oxygen would then be 4.727 calories and the calculated heat output per hour would be 57.1 calories or only a difference of 2 per cent in the final result. The objection to the assumption of a respiratory quotient therefore appears to be of little practical consequence

The comparison between the two methods of determining the heat output of Miss A A was carried out on five different occasions and it was noted that on all occasions the R Q was different in the first and second open-circuit experiments The results are given in Table II There was no question that Miss A A was unaccustomed to the test for by the time these experiments were carried out she had taken part in 700 similar tests These results seem to confirm what Benedict (personal communication) has maintained that the introduction of a mouth piece and nose-clip or the application of any face appliance alters the carbon dioxide output and thus vitiates the measured respiratory quotient in short-period experiments It appears therefore that by assuming a R Q of 0 82 a correction rather than an error is being introduced into the calculations for the chances are that the measured R Q in a short-period experiment of 10 min is fallacious The above observations suggest that even in the case of a trained subject the carbon dioxide output becomes normal only after the mouthpiece had been applied at least 15 min

TABLE II—*Respiratory Quotient*

	R.Q		R Q
First Douglas bag experiment First observation made	0 90	Second Douglas bag experiment The third observation made the mouthpiece and nose-clip having been applied for 5 min	0 84
	0·78		0 81
	0 74		0 81
	0 755		0 83
	0 73		0 81

Effect of breathing pure oxygen—Objections have been raised to the closed circuit type of apparatus on the grounds that the breathing of pure oxygen alters the metabolism Evidence by Benedict and Higgins (1911) and others has shown that oxygen does not stimulate metabolism

Accuracy of the apparatus during an experiment—With the closed-circuit type of apparatus a test for tightness of the apparatus can easily be carried out during the actual determination The test consists of placing a 50 gramme weight on the spirometer bell and watching for evidence of a sudden fall in the volume of enclosed oxygen This is a most delicate test for a leak No such means can be applied to the open-circuit method, which is a very serious disadvantage

Time involved in the calculations—In the closed circuit method the calculations of the basal metabolism from the kymographic chart of the respirations take about two or three minutes At a glance immediately the test is completed it can be determined whether the test is satisfactory or not and a further reading required In the open-circuit method after the volume of the expired air has been measured and a sample taken the accuracy of this method depends upon the analysis of the sample which is done in duplicate If two determinations have been carried out on the patients this means four gas analyses and in addition the Haldane apparatus must be checked by an analysis of room air The labour and time involved by this necessary procedure is enormous and it is only after this work has been completed that one is in a position to determine that the duplicates of the heat output of the patient agree sufficiently to warrant no further tests

SUMMARY

1 A comparison of the closed and open-circuit methods for determining the heat output has shown that they are both equally accurate

2 The assumption of a respiratory quotient of 0 82 in the closed-circuit method does not appear to introduce any error in the calculations

3 The respiratory quotient obtained with the Douglas bag is probably inaccurate even in a trained subject in short-period experiments such as are commonly used in most laboratories to determine the basal metabolism

4. The closed circuit possesses many advantages over the open circuit in that it is much more rapid and a ready means is available for testing of the apparatus during an experiment

I wish to thank Mr Knott of J W Benson Ltd, Ludgate Hill London, for the advice and help he has so freely given in connexion with the kymographs and Prof E C Dodds for his criticism of this paper

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AUSTRALASIA

(FROM OUR OWN CORRESPONDENT)

FOUNDATION OF QUEENSLAND MEDICAL SCHOOL

FOR the first time in fifty years a new medical school has been founded in Australia the inauguration of the faculty of medicine in the University of Queensland being the first ceremony of its kind since the Adelaide school of medicine was opened in 1885 The oldest school in Australia, that of Melbourne was opened in 1863 the Sydney school following twenty years later

Tropical hygiene and medicine will be a compulsory subject in the undergraduate course of the new school. The fact that roughly half the area of Queensland lies in the tropics accounts for this unusual feature. If as is expected about 40 medical students in each year enter the Queensland medical school there will be a total of over 200 students altogether The numbers attending the older Australian medical schools are Sydney 632 Melbourne 600 and Adelaide 120 Preliminary matriculation is required of all entrants to the medical school of the University of Queensland and the requirements are so framed as to encourage future medical students to study the subjects that will be of most use to them when they enter the faculty Contrary to the usual practice, Latin is not compulsory a choice between French and German being allowed. As the greatest volume of medical literature outside their own language is written in German students are recommended to study that tongue. Mathematics physics, and chemistry are compulsory though only one of the latter two need be taken at the senior standard In the other medical schools of Australia all the institutions necessary to the education of medical students are situated in different parts of a large city thus involving much waste of time in travelling from one to another The Queensland medical school has the advantage of having in Brisbane a 600 bed hospital comprising all the necessary departments including a children's hospital a modern maternity hospital and a hospital for infectious diseases besides providing the usual training facilities of a general hospital. The curriculum of the new school carries out the suggestions made in the recent report of dealt with a lot of poor starved folk brought out of Hongkew and Yangtse Poo, some with old festering wounds Dysentery has become rather bad I think there is little doubt but that it is due to the enormous number of flies which have come over from the destroyed areas, where there have been large numbers of corpses

Police observers aver that immense numbers of Chinese have been herded into alley ways and simply machine gunned down It is very significant that when the public health department demanded passes to get in and collect corpses for destruction the Japanese absolutely refused to let them in, and stated that they were going to do all that themselves Naturally this is taken to mean that they do not want it known what they did in those early days in Hongkew and Wayside, and as we cannot get any real news yet of the Medhurst buildings no one is allowed there We know that vast areas have been burned out

To day there has been furious fighting all along the Pootung shore and across from the Bund The Chinese had brought up guns back in the Pootung area but started out with a lot of snipers, creeping up and opening fire on the Japanese gunboats beside the Garden Bridge and the Japanese consulate nearby Baxter from the Mission buildings and Elliston from a high building near both saw the whole morning's work Three Chinese shells went into the Japanese Consulate Another hit alongside a cruiser There were several shrapnel bursts over a gunboat and a Japanese boat was sunk There is a long line of Japanese gunboats all down the river and they all burst forth plastering the Pootung shores and smashing up godowns and buildings Aircraft were also busy, bombing away The noise was pretty fierce, especially as it was near at hand (It is quite a business trying to telephone with all the row) A shell fell in Peking Road this afternoon but did not do a great deal of damage Nine Chinese and one Sikh were brought in by ambulances

I had a letter from Harmon He and his family are in Hong Kong after an exciting trip down the coast They rescued a Japanese from a scout plane which fell into the sea near by They ran out of water and food and put into Amoy for more After leaving the family at Hong Kong Harmon started out for Shanghai The steamer was caught in a great typhoon and blown ashore Harmon was one of those rescued, and returned to Hong Kong to await another chance of getting here

The third flotilla Japanese Fleet has been firing all day fifty rounds heavy to one Chinese light round Planes dropping bombs all over the place, but when they stopped at 4 30 P M. for tea the two Chinese trench mortars at once revived and restarted, and even the machine gun recommenced at the very place it had first been in!

THE SERVICES

SHORT SERVICE COMMISSIONS FOR DENTISTS

THE War Office announces that applications are invited from dental surgeons for appointment to a limited number of commissions Candidates will be selected without undergoing competitive examination and will be required to present themselves in London for interview and physical examination towards the end of October They must be registered under the Dentists Acts or Medical Acts and be not over the age of 28 Successful candidates will be given short service commissions for six years, when they will retire with a gratuity of £1000, unless they have been granted permanent commissions Permanent commissions will be given to officers selected from those who wish to make the Army their permanent career Particulars of the conditions and emoluments and form of application may be obtained by post or in person from the Director, Army Dental Service, War Office, London, S W 1

ROYAL NAVAL MEDICAL SERVICE

Surg Comdr F H Ward transferred to Emergency List

Surg Lt Comdr R C Foster to be Surg Comdr

Surg Lts (D) N L Parry to *Victory* for R N B D C Howe and W G Smith to *Drake* for R N B , and J B Knight to *Ganges*

Surg Lts (D) for short service W H Bain (Glasgow Dental Hosp) R W Ellis Smith and J B Inverdale (Bristol Univ) and P V Peatfield (Guy's)

Mr C F Hicks of Huntingdon has been appointed Admiralty Surgeon and Agent for Huntingdon Mr J W J Willcox of Glastonbury, for Glastonbury, and Mr R W Riddle of Shoreham, Sussex, for Shoreham

ROYAL NAVAL VOLUNTEER RESERVE

Surg Lt Comdr W H Roberts to R N B Devonport

Proby Surg Lt W I D Scott to be Surg Lt

ARMY MEDICAL SERVICES

Col R C Priest, M D F R C P , K H P , Professor of Tropical Medicine Royal Army Medical College and Consulting Physician to the Army, will be promoted to the rank of Major General (supernumerary), with effect from Oct 13th, 1937, and will continue in his present appointment

Col. Priest received his medical education at Caius College Cambridge and St Thomas s Hospital He joined the R.A.M C in 1909 was promoted major in 1921 brevet lt -col in 1931 substantive lt. col in March 1934, and brevet-col in the next month He was promoted colonel this year He served in India Mesopotamia and Egypt during the Great War He was appointed K H P in 1931 In 1930 he was consulting physician to the military forces in Palestine with the rank of temporary colonel Col Priest was appointed Professor of Tropical Medicine and Consulting Physician to the Army in July this year

ROYAL ARMY MEDICAL CORPS

Lt (on prob) E W O Skinner is restd to the estabt and confirmed in his rank

ARMY DENTAL CORPS

Short Service Commission R C Fraser to be Lt (on prob)

TERRITORIAL ARMY

Lt Col and Bt Col D Dougal M C , from T A Res of Off , to comd 5th (Western) Gen Hosp

Maj and Bt Lt Col L McI Weeks, M C , T D , to be Lt Col and to comd the 1st (Northern) Gen Hosp

Capt A A Eagger, from T A Res of Off , to be Lt Col and to comd 6th (Southern) Gen Hosp

Lt J H Hopper to be Capt

The Efficiency Decoration has been conferred upon the undermentioned officers under the terms of the Royal Warrant dated Sept 23rd, 1930 Lt Col J O Thomas M C , Maj and Bt Lt Col J Marshall, M C , and Maj W R Martine M B E (empld Edinburgh Univ Contgt Sen Div , O T C)

ROYAL AIR FORCE

Wing Comdr H S C Starkey, O B E , is placed on the retired list

Squadron Leader A A Townsend to No 5 Flying Training School, Sealand for duty as medical officer

Flying Offrs promoted to the rank of Flight Lt G B MacGibbon, D F S Shaw, C C Barker, and C E G Wickham

Flying Offr J R McWhirter to No 3 Armament Training Camp, Sutton Bridge, and F V Maclaine to R A F Station Digby

R M Hewat is granted a short service commission as a Flying Offr for three years on the active list and is seconded for duty at St Mary's Hospital

Dental Branch —F C W Rudd is granted a non permanent commission as a Flying Offr for three years on the active list, and is seconded for duty at the Liverpool Dental Hospital

AUXILIARY AIR FORCE

No 615 (County of Surrey) (Army Coöperation) Squadron T Crowley is granted a commission as Flying Offr

THE MEDICAL REGISTER

UNTRACEABLE PRACTITIONERS 1937

We have been requested by the authorities of the General Medical Council to publish the following list of registered medical practitioners who had not when the list was sent to press, replied to letters written to them on behalf of the Council under Section 14 of the Medical Act, 1858 in order to ascertain whether their addresses on the Medical Register are still correct The date given after each name is the date of original registration the qualification given is the principal qualification registered by the practitioner The letters (E) (S) or (I) indicate whether the practitioner was originally registered in England Scotland or Ireland; and the expression (Col.) or (For) indicates that the practitioner is registered in the Colonial List or in the Foreign list in the Register Any practitioner wherever resident who finds his or her name in the list should write without delay to the Registrar General Medical Council 44 Hallam street Portland place London W 1 unless he or she was originally registered in Scotland. Practitioners originally registered in Scotland should write directly to the Registrar of the Branch Council for Scotland 44 Queen-street, Edinburgh 2 The name of every practitioner in the list from whom a further communication is not received at a very early date will be omitted from the next issue of the Register in accordance with the provisions of Section 14 of the Act of 1858

Beard Emile A C, M B, 1913(S)
Booth William, M B, 1925(S)
Bourke, James J F L R C P & S., 1897(I)
Braddon William L, M R C S 1884(E)
Brandon, Arthur J S M B., 1901(E)
Brewis Edward C M D 1923(E)

Carleton, Gladys C. M B 1918(S)
Chisholm Alexander N L.M.S. 1919 (Col.)

Daly Thomas, M B, 1927(I)
Davies Percy V, M R C.S., 1911(E)
Dodson, George E M.R C.S 1897(E)
Durrani, Nisar M M R.C.S 1932(E)

Erskine, William A. M B 1936(S)

Fair Aileen M B, 1926(I)
Fairchild George C M R.C.S 1914(E)
Falkiner, John McI F R.C.S, 1890(I)
Fannin Lewis E. L R C P & S. 1898(I)
Farquharson, Alexander C., M D 1889(S)
Farrar Percy B M D 1921(S)
Farrell Mary J M D., 1916(I)
Fell, Frank J L R.C.P & S 1929(S)
Fernandes Francisco L R.C P & S 1885(S)
Findlater Christina G, M B 1924(S).
Finegan, Laurence P J L R.C.P 1876(I)
Fisher Vicars M, M.B 1910(I)
Fitz-Gerald, Gerald H M R C.S, 1918(E)
FitzGerald William M B 1895(S)
Fitzgibbon Maurice M B 1904(I)
Fitzpatrick Ernest H L R.C P & S 1887(S)
Fleming, (Mrs.) Muriel K, M D 1915(S).
Floyer, Blaise B M R.C.S, 1872(E).
Ford, Donald M L R C P & S 1901(S)
Fordham Henry J L.M.S.S.A 1927(E)
Forster William A de V, M D 1901(I)
Forsythe, Charles, M D 1873(I)
Fowler William M M B, 1914(S).
Fox, Percy H, M R.C S, 1928(E)
Froebairn Robert J, M B 1887(S)
Freeman Joseph L R C P & S 1899(S)
Freer, Robert M M.B 1895(S)
French Alexander M., M R.C S 1874(E).
Fullen, Patrick L L R C.P & S. 1932(I)
Fullerton John A M.B., 1925(S)

Gallleton Alfred T, M B 1898(S)
Galbraith Hugh T L R C.P & S., 1891(I)
Gamble, Annie M, M B., 1925(I)
Gane, Noel G C, F R.C.S, 1923(E)
Gardiner John, M B, 1911(I).
Garland John C M R.C.S., 1934(E)
George Henry, M R C.S 1837(E)
Giblin Arthur L, L.R.C.P & S 1910(S)
Gill, James W M B 1921(S)
Giusani, Joseph, M.S, 1884(I).
Gluck Susan M B, 1924(E)
Glynn Eric H, M R.C.S 1925(E)
Goggin Edward, M.B., 1926(E)
Goldsworthy Bertha H (formerly Lawler) M.B 1924(I)
Gool Goolam H M R.C.S., 1931(E)
Gore, Lionel (formerly Gorfunkle) M.B 1932(I)
Gouldesbrough, Claude, B.M, 1909(E)
Gouws, Johan N B., M B 1926(I)
Gow Archibald M D 1901(S).
Grace Jeremiah L.R.C P & S, 1906(I)
Greer Andrewanna P, M B, 1923(E)
Griffin Blanche G C M B, 1911(I)
Griffiths Arthur V, M R C.S. 1934(E)
Gunn John C M B, 1927(S)
Gurney Arthur L M B 1901(S).

Hall Arthur J M B, 19[illegible] (E)
Hall George J A L.R C P & S 1891(I)
Hall Phillis, M B., 1923(E)
Halloran Kathleen M M R.C.S. 1926(E)
Hamilton, Dennis G M.R.C.S 1928(E)
Hammer Norman W, M R.C.S., 1924(E)
Hannan, Mary J., L.R.C P & S., 1890(I).
Harbinson, James W., L.R.C.P & S. 1888(I)
Harbison Henry A., M.B., 1914(I)
Hardaker Frederick G B L.M.S.S.A., 1927(E)
Harper Rodolphus W M B., 1908(I)
Harris Arthur G R., M R C.S 1871(E)
Harris, Bernadotte, L R C.P & S 1893(E)
Harris David B L., M B, 1929(I).
Harrison, Charles, M R C.S., 1883(E)
Harse Eleanor M.B., 1921(E)
Harwood, Harold M., B Chir, 1900(E)
Hay Thomas H F R.C.S 1894(S).
Hayes, John J L.R.C P & S 1918(I)
Hayes William B., M.D, 1886(I)
Head, Ernest E M R.C.S 1895(E)
Hecker Cyril F., M R.C S., 1929(E).
Heffernan John T L R C.P & S 1910(I)
Hebron George M, M R C.S, 1912(E)
Heinshberg Pearl M M.R C.S., 1933(E)
Heiser Arthur L, M.R.C.S, 1904(E)
Helmy Ali, M R.C.S., 1925(E).
Hendry John M M.B 1908(S)
Herridge (Mrs) Margaret A L (formerly Buckner) M B., 1926(E)
Hessey James D., M R C.S 1892(E)
Heyer Fritz G., L R.C P & S 1903(S).
Heywood, Thomas, M.R.C.S., 1892(E)
Hickey Patrick C, M D, 1880(I)
Hickley (Mrs.) Edith M P (formerly Morris), M.B., 1918(E)
Higgins Edward J L.A H, 1920(I).
Higgins Hubert M R.C.S 1888(E)
Hill, Wilfred A M.B., 1931(I).
Hinde Alfred B M R C.S., 1886(E)
Hobson Edward L. M B 1913(I)
Hocken, Donald F., M B 1921(E).
Hogan Mary G, F R C.S. 1922(I)
Holmes, Bernard W, M R.C.S., 1898(E).
Hoops Samuel E., L.R.C P, 1876(I).
Hopkin Denis A B., M R C.S 1935(E)
Horsham, Joseph, L R.C.P & S., 1925(S)
Hosny Mostafa H M R.C.S. 1934(E)
Hough Herbert B., M R.C.S., 1930(E).
Howard, Henry, M B., 1880(E)
Hugo Daniel, M B., 1922(I).
Humphry Herbert V L.M.S.S.A., 1921(E)
Hurley Cecil E., M B, 1925(I)
Hutchens, Harold J M R.C.S, 1899(E).
Hynes Thomas G., M.B., 1930(I)

Iredale Jabez P, M B., 1891(E).
Ismail Ali M.R.C.S., 1927(E)
Iyengar, Mandayam A. P L.R.C.P & S 1919(S)

Jack, Alexander F., L R C.P & S. 1900(S)
Jacobs Martin H M.R.C.S 1921(E)
Jaggassar Leonard O L.M.S.S.A. 1927(E)
Jain Banarsi D L.M.S.S.A 1927(E)
James Samuel, L R.C.P & S, 1935(E)
Jameson Ernest T, M D 1907(I)
Jamieson Archibald L.S.A., 1887(E)
Jansen van Vuuren Miriam M.B 1931(S)
John David M R.C.S., 1883(E)
John Thayil C, L R C.P & S, 1932(E)
Johnson Alfred M D 1897(E)
Johnston Hugh C A M B, 1933(I)
Johnston, William M.B 1921(I)
Jones Aneuryn M M R.C.S., 1927(E)
Jones, Daniel M M B 1882(E)
Jones Wilfred H G., M.B, 1935(E)
Jones, William W, M.R C.S, 1900(E)
Jowell Abraham M R.C.S 1924(E)
Jubb Archie V M.R C.S 1905(E)

Kahn, Abraham L., L R C.P & S. 1933(S).
Kak, Jainath M B, 1931(E)
Kamchorn Nai, M R.C.S 191 (E)
Keenan, Edmund J, M B, 1920(I)
Keess, Arthur M.R.C.S, 1883(E)
Keiller William, F R.C.S, 1888(S)
Keith, Hugh, L R C P & S., 1893(S)
Kelavkar Tarabai L R C.P & S. 1928(S)
Kelleher Julia L., M B 1915(I)
Kelly Edward P, L R.C.P & S 1927(S)
Kelly Michael, M.S, 1883(E)
Kelly, Phyllis J, L R C P & S., 1925(I).
Kelsall, Henry T, M D 1880(E)
Kendall Ernest H., M.S, 1895(E)
Kendall John W M R.C.S, 1926(E)
Kennedy Francis P L R.C P & S 1913(I)
Kennedy Frederick W, M.D., 1891(I)
Kennedy Patrick J, M B, 1925(I)
Kennedy Roger A M R.C S 1928(E)
Kerrigan Sarsfield P, M.B., 1910(I)
Khan Abdul Hamid, M.R.C.S, 1934(E)
Khan Mohammad B., M B, 1934(E)
Khishin, Anis E S E L.R.C.P & S., 1932(I)
Killen Mary J S M.B, 1923(E)
Kilroe Sidney H J., M B., 1908(E)
Kincaid Frederick M R.C.S., 1902(E)
King Douglas M M B., 1934(E)
King, Edward F, M B, 1920(I).
King Gerald G, M.R C.S, 1928(E)
King, Thomas H V., M R C.S 1915(E)
Kirkland Gerald B M R C.S, 1923(E)
Klein Andrew J V L R.C.P & S 1934(E)
Knight, Robert G M R C S 1932(E)
Knowles, Robert, *C.I.E* M R.C.S. 1907(E)
Kohler Theodor C M R.C.S., 1928(E)
Kreitmayer Maximillian, M.R.C.S., 1928(E)
Krige Johannes F van W M.B., 1924(E)

Lacey Jack W., M R C.S., 1935(E)
Lamech, Jesudasan S L R.C.P & S 1919(E)
Lanceley Hilda I, M.R.C.S., 1934(E)
Lane Alexander, F R.C.S. 1881(E)
Lassalle, Charles F., I S O., M.D, 1902(E)
Laurence, Noel F., F.R C.S, 1924(E)
Lavin, Michael F, M B 1919(I)
Law John L, M B., 1909(S)
Lawson, William B L.R.C.P & S. 1916(S)
Leach Herbert, M R.C.S., 1901(E)
Leigh Frank B, M B, 1905(E)
Leigh Barlow Vivian H L R C.P & S., 1927(S)
Leventhal, George, M D, 1932(S)
Lewin Bruce F M R.C P 1928(E)
Lienkmo, Theophile J L.M.S.S.A. 1923(E)
Lindsay, David A., M B 1934(I)
Lloyd John T., M R.C.S 1904(E).
Lochhead William K. L R.C.P & S. 1888(S)
Loewenthal Max S. M R C.P 1895(E)
Logan Roderick R. W., M.R C.S 1890(E)
Long Joseph J., M D., 1891(I)
Low Eugene W, M.B 1933(S)
Lowsley Lionel D., M

the trained mind of the philosopher look upon the teaching of Freud ? "Cyril,' I shouted, "What do you think of that particular brand of psychology known as the psycho analytical school ?"

He came up to me "I think nothing of it," he answered, taking his pipe out of his mouth so that he could punctuate his further remarks with its stem "A corner-stone of Freud's teaching is the theory of the unconscious or subconscious mind Now the subconscious is only revealed through the conscious, and when you know a thing from that moment it ceases to be unconscious Our knowledge of the subconscious is by deduction and inference like our knowledge of God Being based on an inferential process the ideas are clearly subjective If psycho analysis were indeed true its principles would not be objectively valid but would merely be a reflection of the psycho analyst's own unconscious desires This being so "

I interrupted him Undiluted logic is liable to go to the head of the illogical as wine to that of the teetotaller If I were to listen to any more I would become confused and be in need of analysis myself "Thank you very much, I interjected, "that was exactly what I wanted to know" "And what do you think of it *yourself*," politely asked my host, replacing his pipe to his mouth

"The psycho analytical school is a cul de sac into which too many people have fallen," I answered "Once in the sac they spend the rest of their days in the happy pursuit of collecting old labels and inventing new ones"

"By that you mean ?"

"Complexes, mother, father, castration—dozens of them It's a lovely game"

My host nodded and left me When two people reach agreement conversation must inevitably come to an end

* * *

But the proof of the pudding is in the eating of it Heaven knows that a great deal of medicine is based on bad logic and that if every remedy of an empirical nature had to be put into the dustbin very little treatment would remain What are the results of psycho analysis ? The answer is that the results are the same as with any other form of treatment that is based entirely on empiricism—namely, the obtaining of a few successes, some doubtful benefits, and many failures But unfortunately what makes things infinitely worse in the case of analysis is the fact that in order to qualify for this hazardous gamble a patient must agree to an initial act of faith—namely, agree to put himself into the hands of an analyst who will require his presence in his sanctum five days of the week, for an indefinite number of years ! Hard is the way and narrow is the gate that leadeth to salvation

* * *

And yet, as a controversy that recently broke out on the pages of this journal clearly brought out, there are many who feel that this is the gate through which we must all pass in order to reach sanity "I agree that firm adherence to scientific principles was never more necessary than it is in psychotherapy to day," writes one of these controversialists,[1] "but shall we get it by handing psychotherapy to the clergy ?"

Do I hear the voice of a Jesuit denouncing a heretic or of a heretic denouncing a Jesuit ? It matters not which, the voice is as old as mankind, the words change with the centuries but the tone is the same

Do not let it for one moment be supposed that I do not recognise the importance of psychology in medicine It is because I regard it as so important that I deplore the inefficacy of that particular brand of psychology that at the present day has gained the ascendancy in psychotherapeutists Nor am I alone in my pessimistic view of the state of psychology in general Those who have read the latest of Prof McDougall's books will remember that this great authority is equally suspicious of what is so easily mistaken for progress in psychology, for he leads us to believe that most of our present theories will have to be scrapped if we are to begin to advance We must wipe the slate clean and start again

But the doctor's dilemma is only a particular instance of one that is general in the modern world The medical man has no philosophy to offer his patient because the modern world has none to offer him Overwhelmed by the flood of disjointed observations, measurements, deductions, and inferences, of which science is made up, he has no time to search for any understanding of the whole Dazzled by its spectacular successes in the material plane, he forgets how little it can help him in that far more important plane of his inner life He is without a message for his patient

The subject I have chosen for these reflections—namely, the relationship of philosophy to medicine—can easily be disposed of It has *no* relation I will pocket my paper and pencil and go for a walk in the country

INFECTIOUS DISEASE

IN ENGLAND AND WALES DURING THE WEEK ENDED SEPT 18TH, 1937

Notifications—The following cases of infectious disease were notified during the week Small pox, 0 , scarlet fever, 1868 , diphtheria, 1308 , enteric fever, 39 , pneumonia (primary or influenzal), 392 , puerperal pyrexia, 115 , cerebro spinal fever, 39 , acute poliomyelitis, 54 , acute polio encephalitis, 10 , encephalitis lethargica, 5 , continued fever, 2 , dysentery, 32 (5 at Luton), ophthalmia neonatorum, 1 (Lambeth), 94 No case of cholera, plague, or typhus fever was notified during the week

The number of cases in the Infectious Hospitals of the London County Council on Sept 24th was 2789 which included Scarlet fever, 602 diphtheria 856 (diphtheria carriers 17) measles 92 whooping-cough 362 puerperal fever 11 mothers (plus 7 babies) encephalitis lethargica 283 poliomyelitis 11 At St Margaret s Hospital there were 17 babies (plus 6 mothers) with ophthalmia neonatorum

Deaths—In 124 great towns, including London, there was no death from small pox, 2 (0) from enteric fever, 3 (1) from measles, 4 (1) from scarlet fever, 12 (5) from whooping cough, 27 (6) from diphtheria, 47 (9) from diarrhœa and enteritis under two years, and 17 (1) from influenza The figures in parentheses are those for London itself

Walthamstow and Liverpool each reported a death from enteric fever Of the 21 deaths from diphtheria outside London 5 occurred at Manchester and 4 at Liverpool Portsmouth reported 2 deaths from scarlet fever Diarrhœa was fatal in 6 cases at Birmingham 5 at Manchester 3 each at Liverpool and Newcastle-upon Tyne

The number of stillbirths notified during the week was 253 (corresponding to a rate of 30 per 1000 total births), including 10 in London

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POLIOMYELITIS IN ESSEX —Ten cases of acute polio myelitis were notified in the geographical county of Essex in the week ended Sept 11th The average number over the last ten weeks has been 5 and for the current week it is 4 Of the three county borough in the county only West Ham had a case to report, but 15 of the urban and rural districts reported cases Dr W A Bullough tells us they were all sporadic and no connexion could be traced between any of them

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[1] See *Lancet*, July 31st, 1937, p 288

NATIONAL HEALTH CAMPAIGN

THE following are extracts from articles contributed by medical men to the special National Health Number of the *Times* published on Sept 30th in support of the Government s campaign

Sir Farquhar Buzzard on the Doctor in the Home

the functions and responsibilities of the family doctor of the future must be somewhat different from those of his predecessors He must assume more responsibility for maintaining the health of his clients and for recognising signs of incipient illness physical or mental he must be in a position to give more time to those suffering from what appear to be minor ailments and be ready to hand over in many instances, the care and treatment and investigation of those who are seriously ill to institutions and expert specialists. He will however have a prescribed right to the help that clinics and hospitals can give him and a definite position in the organised scheme of health services of the district in which he practises.

Sir Arthur MacNalty on British Public Health Services

Progress in national health cannot be made without public support The run of a piece in the theatre is short if it is played to empty houses health services without a clientele willing and ready to make use of them would be disastrous How is the support of the people of this land to be secured in the campaign for national health? First of all comes the medical practitioner He is the foundation of a medical service its pivot its anchor its instrument

Dr J M Mackintosh on Scottish Services

Ruskin defined the true aim of national economy as the producing as many as possible full breathed, bright-eyed and happy hearted human creatures ' Dismissed as an irrelevant futility by the economists of the sixties his conception has become the inspiration of modern health policy

Sir George Newman on Health of the School child

Yet even to-day not much more than half the children requiring dental treatment actually receive it. Why is that? Ten per cent of school-children suffer from some degree of defective vision but only half of them are adequately treated Why is that? The answer to this question in both cases is not that the State or the local authority have been neglectful or unready but that the parents or guardians of the child have not taken the trouble to get their child properly treated The school doctor has done his part the means of treatment await the child but the child or its parents are not willing or do not persevere with the treatment or do not understand its importance. The child, all too often, lacks the persuasion or encouragement or support of its home It learns hygiene at school but discovers, not seldom that it is not practised at home

Dr Noel Bardswell on Prevention of Tuberculosis

If one follows the life-histories of a number of patients treated in a sanatorium one sees that for most of them the issue of success or failure is determined during the first year after their discharge Tuberculosis is essentially a social problem The extinction of tuberculosis will be achieved in proportion as these social and economic problems have been satisfactorily met It is in the realisation of this that Care Committees usually composed of voluntary workers, have become an essential factor in our antituberculosis schemes.

Sir Edward Mellanby F R S on Medical Research

The Medical Research Council is of its kind unique throughout the world and it is pleasant to think in these times when political systems are being much discussed and democratic forms of government are often described as effete that this national organisation whose sole function is to advance knowledge for the maintenance of health and the elimination and cure of disease was founded and is maintained by a democracy

Mr J D King Ph D L.D S on Care of the Teeth

It is clear therefore that the scourge of dental disease can best be fought first by increasing the consumption of those foods which will build up strong well-developed teeth, and secondly until this nutritional measure has taken effect by increasing the staff and scope of the school dental service so that yearly—or even half *yearly—inspection and* treatment of both permanent and deciduous dentitions can be provided until the age at which National Health Insurance benefit can be obtained

Dr G F McCleary on Safer Motherhood

The first school inspections still show a wide prevalence of preventable physical defects Increasing attention is being given to the problems of pre-school life and it is generally agreed that among the agencies working for the well being of the pre-school child a prominent place—perhaps the most prominent place—should be given to the nursery school The number of nursery schools so far established is however very small fewer than a hundred in England and Wales Many more are badly needed.

Dr Melville D Mackenzie on Recent Trends in Physical Culture in Other Lands

the old body building school which was concerned only with physical development is being superseded by the natural school which aims at self-control and adaptability to environment Formal gymnastics and systems of physical culture are everywhere giving way to field sports camping and free exercises. The old so-called Swedish system is being modified so as to abolish periods of immobility and to introduce movements inspired throughout by nature—walking running jumping climbing crawling wrestling and swimming are the principal features In this, as in other modern systems of sport the aim is to develop endurance and resistance to fatigue cold and pain the ultimate object being to build up the complete athlete not specialised in any way In Norway particularly, stress is chiefly laid in training on the fundamental importance of developing in the individual those aptitudes for forms of sport which he appears to lack. Hence the setting up of records or specialisations in games is discouraged.

Dr A Macrae on Child Guidance

Certain it is that the medical historian of the future will describe the twentieth century as a time when the doctor too long preoccupied with physical disorders achieved a new understanding of mental conflicts and anxieties and a more effective method *of treating those distressing* and disabling nervous *conditions* which can be classified neither among the organic bodily diseases on the one hand *nor* among the insanities on the other

The Medical Correspondent of the Times on Food and Health

Food habits have changed greatly during the past half-century Among the causes of change are the more extensive use of machinery in place of manual labour *a rising standard of living* and the processes of refrigeration and preservation

Mr H L Eason on Voluntary Hospitals

The essence of all advance in medicine and surgery is individualism, heterodoxy and freedom of action. These three virtues do not so far as experience has shown flourish under public systems of *administration*

Dr Drummond Shiels on Teaching and Treatment (of *Venereal Disease*)

Comparing 1936 with 1920 there was a *reduction* of 50 per cent in the total number of cases of syphilis (old and new *infections*) dealt with at the treatment centres in England and of 28 per cent in the total number of cases of venereal disease *The* latter figure rightly suggests that there has not been the same degree of success in the case of gonorrhœa Many infected women, especially, fail to seek treatment

Dr W M Frazer on Port Sanitation

Port sanitation is one of the oldest branches of preventive medicine, and the earliest quarantine laws against plague date back as far as the year 1348, when this disease was present in epidemic form in Europe

Dr I Harvey Flack on the National Eye Service

The vague but hopeful term "limited means" is as widely interpreted as the scope of the service is generous Frames, which may be of nickel or rolled gold or imitation tortoiseshell, and are not important, and lenses correctly prescribed and accurately ground, which are of vital importance to national eyesight, are available to all the many non insured persons whose incomes do not exceed £250 a year, to all the compulsorily insured classes irrespective of income, and to their dependents

* * *

The Prime Minister contributes a message calling attention to the rapid development of the public health services within recent years, and the other contributors include Sir Kingsley Wood on the March to Health, Mr John Rowland on Welsh Services, Lord Stanhope on Health and Home, Lord Baden Powell on Aims of Scout and Guide Movements, Prof Ernest Barker, D Litt, on Community Centres, Sir Lawrence Chubb on Playing Fields Mr Alexander Paterson on Clubs for Boys, Colonel G N Dyer on Mental and Physical Training in the Defence Services, Miss Prunella Stack on Physical Culture for Women, Lady Eleanor Keane on Girls' Clubs, Lord Aberdare on Building a Healthier Nation, Sir Iain Colquhoun of Luss on Scottish Plans, Sir Laurence Brock on Mental Health Lord Balfour of Burleigh on Houses and Homes, Sir Hugh Jeudwine on Duty and Discipline, Mr Robert R Hyde on the Health of the Worker, Mr W W Vaughan on Sound Citizenship, Mr Henry Lesser on National Health Insurance, and Mr Douglas Kennedy on Dancing for Joy

PUBLIC HEALTH

A Health Centre for Southwark

THE Walworth road is generally regarded as one of the most unlovely thoroughfares in south London The names of the roads leading into it show that a large part of the area was first developed shortly after the battle of Trafalgar, but much of the surrounding borough of Southwark is far older Things like prisons and slaughter-houses which were considered unsuitable in the City of London had to find a place on the south side of the river, and for centuries foul conditions have been harboured there so that no part of the capital has had a more uphill fight to improve the environment of the people Even in recent times the death rate has been the highest in London and the state of overcrowding has been appalling On Saturday last a further step forward in the organisation of the public health services was taken by the opening by the mayor of Southwark of a new building to bring them together under one roof It has been erected alongside the public library and town hall in the Walworth road, at a cost of £50,000 Accommodation is provided for the medical officer of health (Dr William Stott) and the public analyst (Mr C Dickinson) and their staffs The old tuberculosis dispensary will be closed and moved into this building which has provision for X ray examinations, dental treatment, and an artificial pneumothorax clinic The solarium is a new departure and is well equipped for the application of light heat, and electrical energy The maternity and child welfare department is on the ground floor with a convenient separate entrance for perambulators A feature of the work of the department is to be an educational section in which lectures illustrated by cinematograph films will be given and exhibitions held in connexion with public health A descriptive account of the public analyst's work circulated to the visitors at the opening traces attention to adulteration back to THE LANCET Sanitary Commission in the middle of the last century and records the remarkable fact that "of all the ports in the country Southwark imports the second largest quantity of foodstuffs per year"

The borough council have wisely decided that the building shall have a pleasing appearance and by the brightness of its interior give a cheery welcome, so that the inhabitants may be encouraged to make full use of an institution devoted to the improvement of their health

The Southwark health centre

"Before School Age"

The London Council of Social Service which aims at examining the adequacy of the social services of the metropolis, has devoted its first survey to the provision made for children under school age, and the results of the inquiry are embodied in a report obtainable from the Council at 7, Bayley street, W C 1 The service investigated is that normally required by little children simply on account of their age and condition, apart from defect, sickness, or casualty, the principal activities concerned being maternity and child welfare centres, nursery schools, day nurseries and the service of health visitors in the homes Most of the welfare work for young children had its origin in voluntary effort and voluntary agencies still take a prominent part in carrying it on in partnership of one sort or another with public authorities

Up to a point the facts disclosed by the investigation must be considered satisfactory The health of children has undoubtedly improved in recent years and it is only fair to give some of the credit to the increased social services Over the whole London area health visitors are at work in the homes and a network of welfare centres provides medical advice and minor treatment Nearly all boroughs supply cheap milk for needy cases and in 22 out of 29 boroughs day nurseries exist where mothers may leave their children while they are out at work A less satisfactory situation appears when the various boroughs are compared Bethnal Green with an estimated child population of 8266 has only two child welfare centres whereas Bermondsey has eleven and Camberwell ten for child populations of 11 388 and 15 812 respectively The number of nursery schools is obviously inadequate the total in the whole London area being nineteen of which sixteen are voluntary and three established by the London County Council The disturbing facts came to light that apart from dental cases 13 8 per cent of school entrants required immediate medical treatment affections of ear nose and throat being the commonest complaints while more than 9 per cent needed treatment for severe dental decay The position seems to be either that facilities for pre-school children in London are inadequate or that insufficient use is made of them It was not possible to obtain statistics of attendance at welfare centres in the various age-groups though it was evident that the service is more freely used by children under one year than later While it is obviously not easy for a mother burdened with home and family cares to attend regularly at a centre such a mother is precisely the one who needs the help and education which the centres provide and all efforts should be made to adapt the service to her requirements

The Council suggests that the first means of improving the service for London children should be to concentrate the whole system under one authority—the London County Council. At present the education authority is responsible for the provision and assistance of nursery schools, while the other services are in the hands of the borough councils an arrangement that tends to interfere with continuity of medical service A uniform policy for London as a whole would the writers of the report believe raise the standard in backward areas remove the danger of overlapping and facilitate the keeping of comparable records throughout the county The report further recommends an increase in the number of health visitors and suggests that improvement in the distribution convenience and attractiveness of welfare centres and a uniform nutrition service in the shape of milk for young children might overcome the reluctance of parents to avail themselves fully of the advantages offered

CORRESPONDENCE

CONTINUITY IN ORTHOPÆDICS

To the Editor of THE LANCET

SIR,—In your leading article of Sept 11th you discussed certain difficulties I had found in my work at the Willesden Orthopædic Centre Mr Tippett admits he has not read my report on the work at this centre and this is unimportant since your references to it are strictly accurate but it is unfortunate that he has not read your leading article with more care He says that one cannot keep every patient under supervision indefinitely Quite true—but what I said was that in *a small group* of cases observation should be continued long after completion of treatment I had thought this so obvious that only one supporting example was given; but since it is remotely possible that Mr Tippett may not be alone in opposing this recommendation it might be wise to deal at length with the various groups of cases in which prolonged observation *is of* value. They are as *follows*: conditions in which late relapse *may occur*—e.g joint tuberculosis conditions in which there may have to be a long delay before operative treatment can be undertaken—e.g stabilising operation for infantile paralysis; cases in which a comparatively new form of treatment has been employed the value of which has not yet been accurately assessed—e.g synovectomy for chronic arthritis; and diseases in which knowledge of the natural history is still fragmentary—e g dyschondroplasia. In practice the total number of cases involved is not great but for all but the surgeon who regards his patients merely as birds of passage most important.

Few of us feel as confident as does Mr Tippett about the end results of treatment of congenital dislocation of the hip and I should like to know the facts on which he bases his opinions It is I suppose *too* much to expect that he will help us by publishing any extensive series of cases since on his own showing he has no use for follow up work.

To suggest that prolonged observation of cases is an admission that a surgeon is afraid to commit himself to saying that a patient is cured, or that nothing further can be done for him shows lamentable lack of vision What one says to the patient and what one thinks about the purely surgical aspect of the case are not always the same thing There are so many things about which we are not yet quite sure. At one time the late Mr Trethowan taught and wrote that his reconstruction operation for Pott s fracture gave splendid results, but prolonged observation showed that osteo arthritis of the ankle almost always *developed sooner or later* and he was compelled to abandon the operation. One could multiply such examples almost endlessly Conversely a condition that has been abandoned as incurable may suddenly come within the scope of some new form of treatment An historic instance is Raynaud s disease.

Mr Tippett believes that another factor destroying the value of follow up work is that most of us try to gloss over our failures and are therefore incapable of assessing end results without bias There is a grain of truth in this, but I am sorry that this thought is *uppermost in his mind.* I may be a foolish optimist but I have sufficient faith in my brethren to believe that we are slowly acquiring something of that scientific detachment so essential to the progress of medicine. And thank heaven it is not incompatible with regarding our patients as human beings and not merely as cases.

I am Sir yours faithfully

H J SEDDON

Royal National Orthopædic Hospital, Stanmore
Middlesex Sept [illegible]th

ARSENICAL INTOLERANCE AND THE TREATMENT OF TRICHOMONAS VAGINALIS INFECTION

To the Editor of THE LANCET

SIR,—In your issue of Sept 18th Dr C G H Campbell reported a case in which a generalised exfoliative dermatitis followed the treatment of a *Trichomonas vaginalis* infection of the vagina with the pentavalent arsenical compound acetphenarsine—Stovarsol A patient treated at the St Mary's Hospital venereal diseases clinic a short time ago exhibited a similar toxic eruption, and this case, too, may be of interest

The patient, aged 30 was treated for chronic vaginitis with Stovarsol vaginal compound Two of the 4 grain tablets were inserted into the vagina every night for a fortnight, after which the dosage was reduced to one tablet every night Seven weeks after treatment had begun, the patient appeared at the clinic with a severe and irritating papulosquamous dermatitis affecting the face, neck, trunk, and limbs as in Dr Campbell's case The stovarsol was stopped and the usual methods for elimination of arsenic employed, together with a fat free diet and a sedative lotion for local application to the eruption A fortnight later the condition of the skin had cleared, recovery being uneventful

This case differs from Dr Campbell's in that there had been no previous arsenical treatment and that the eruption appeared a considerable period after treatment had commenced, also recovery was rapid once the administration of the stovarsol had ceased Apparently, therefore, this patient was not hypersensitive to the pentavalent arsenic but suffered from the products of absorption It is the practice at this clinic to instruct patients to use a vaginal douche every morning during treatment with the stovarsol preparation This particular patient lived in the country and also had not the privacy to carry out these instructions Hence there must have been continuous absorption of arsenic during the seven weeks The preparation is used a great deal in the St Mary's Hospital clinic and this is the only case of its kind in the last eighteen months I think it is reasonable to assume that cases showing such a reaction have been avoided by the routine of stovarsol tablets being used at night, followed by a cleansing douche in the morning with no insertion of tablets again till the night

Dr Campbell writes only of a hypersensitive patient, and one whose hypersensitivity had possibly been increased by the previous administration of arsenic The case I have outlined suggests that his warning about the use of this kind of drug and its possible toxic effects applies also to the non hypersensitive patient In addition it may point to the fact that routine treatment as described, minimises any such likely effects and enhances the value of this extremely efficient preparation

It is with the kind permission of Dr McElligott, director of the venereal diseases clinic, St Mary's Hospital, London, that I am able to report this case

I am, Sir, yours faithfully,

M C W LONG,
Clinical Assistant Venereal Diseases Clinic,
St Mary's Hospital, W

Sept 27th

PROTAMINE INSULIN

To the Editor of THE LANCET

SIR,—In response to a demand from users of protamine insulin (with zinc) for a preparation of higher unit value than the 40 units per c cm , the four British firms engaged in its manufacture (Allen and Hanburys Ltd., Boots Pure Drug Co , Ltd , The British Drug Houses Ltd., and Burroughs Wellcome and Co) have now made available a suspension containing 80 units per c cm This preparation is issued in one size only—i e , 5 c cm vials containing 400 units (80 units per c cm) The original preparation containing 40 units per c cm will continue to be issued as at present in 5 c cm and 10 c cm. vials

We are, Sir, yours faithfully,
ALLEN AND HANBURYS LTD ,
BOOTS PURE DRUG CO , LTD ,
THE BRITISH DRUG HOUSES LTD
BURROUGHS WELLCOME AND CO

Sept 24th

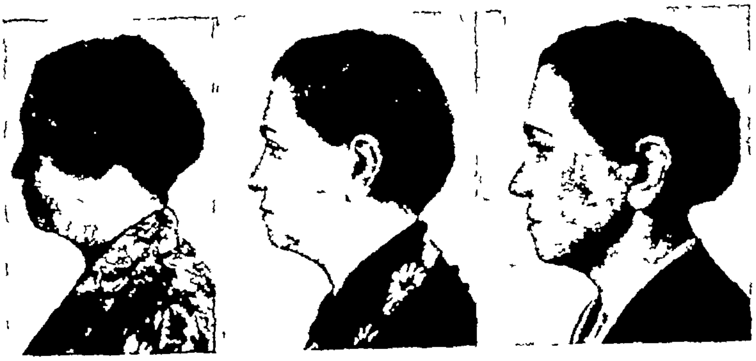
ŒSTRIN IN TREATMENT OF CUSHING'S SYNDROME

To the Editor of THE LANCET

SIR,—Dr Morton Gill's statements in your issue of Sept 4th seem to me disputable, and I would like to comment on them further

(1) Dr Gill was unable to reduce the raised blood pressure or the obesity in cases of Cushing's syndrome by administration of Progynon B I have stated that progynon B therapy, if administered intensively and for a longer period than he used will reduce both the systolic pressure and the obesity This is illustrated by the following case —

The patient was a woman aged 37, with hypertension and regional obesity The accompanying photographs show her facial appearance before therapy (left), after five months' administration of progynon B (centre), and after another five months' treatment with progynon B and proluton (right) (The scars and telangiectases were the result of X ray irradiation for facial hypertrichosis) The improved appearance of the skin as well as the disappearance of the plethoric obesity of the face is apparent *Without diet regulation this patient lost 20 lb , and the* systolic pressure was reduced from 158 mm of mercury to 120 mm



(2) I have not found it difficult to decide when menses should be occurring in cases of Cushing's syndrome with amenorrhœa or irregularity of menstruation The recurrence or the exacerbations of the headaches are informative When ovulation should occur the less severe headaches appear or the existing headache exacerbates for a short period,

specimens in this group were obtained by heel or venous puncture, since cord blood sampling was frequently overlooked in these babies.

Of 25 stillborn infants, samples were examined from 21, or 84 per cent.

The 4 term infants who died neonatally were registered in the delivery room book as neonatal deaths. As it is not uniform practice to register the death of such babies, the actual size of this group is not known, but probably does not exceed 6.

The method used for typing was as follows: A light saline suspension of cells from a clotted blood specimen was made, and then centrifuged for one minute in an Adams Serofuge. The supernatant solution was decanted, and the cells were resuspended in the residual fluid. A drop of this suspension was placed in each of two depressions on a porcelain spot plate. A drop of commercial anti-A serum was added to one depression, and a drop of anti-B serum to the other. After mixing, the suspensions were allowed to stand at room temperature for five minutes, following which they were examined for macroscopic clumping. About 1 per cent of such tests required microscopic confirmation. In general, little difficulty was experienced in evaluating the reactions.

The significances of the observed differences in blood group frequency in the full-term, premature, and stillborn infants were determined by the chi-square method, in a manner similar to that of previous investigators (Buckwalter and associates[11]).

RESULTS

The results are summarized in four tables. Table I lists the A-B-O group frequencies in the 1,033 full-term infants, as well as similar information on 693 pregnant women from the City Hospital clinic. Comparison of these two series does not show any significant difference between them. Chi-square for the comparison of all four groups was 3.55 (3 degrees of freedom). For the comparison of groups O and A in both series, X^2 was 1.28, while for the comparison of O and B it was 1.04 (1 degree of freedom).

The obstetrical patients of City Hospital are predominantly Negro, as is indicated by the fact that 83.0 per cent of the full-term babies, 78.0 per cent of the premature infants, 85.7 per cent of the stillborn infants, and 82.2 per cent of the pregnant women were Negro. For this reason Table I also includes the results of several typing studies of American Negro populations.

Table I. The Frequencies of the A-B-O Blood Groups in 1,033 Full-Term Infants Delivered at Cleveland City Hospital (83 Per Cent Negro) Compared With the Frequencies of Those Groups in 693 Pregnant Women Attending the City Hospital Obstetrical Clinic (82 Per Cent Negro), and in Reported Series of American Negroes

	TERM INFANTS CITY HOSPITAL	PREGNANT WOMEN CITY HOSPITAL	CLEVELAND* NEGRO MOTHERS[18]	HOWARD UNIVERSITY NEGROES[19]	NEW YORK NEGROES[20]	BALTIMORE NEGROES[21]
INDIVIDUALS	1,033	693	2,200	2,495	730	605
BLOOD GROUPS	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
O	47.6	50.5	47.2	51.9	44.2	47.6
A	25.8	23.8	27.1	27.3	30.3	28.3
B	22.5	20.9	22.7	17.3	21.8	20.0
AB	4.2	4.8	3.0	3.0	3.7	4.1

*University Hospitals of Cleveland.

TABLE II. ONE HUNDRED PREMATURE LIVING INFANTS AND 21 STILLBORN INFANTS ANALYZED BY BIRTH WEIGHT, SEX, RACE, AND A-B-O BLOOD GROUP

BIRTH WEIGHT (GRAMS)	CLASS	BLOOD GROUP																				TOTAL OF FOUR BLOOD GROUPS				
		O					A					B					AB									
		N	W	M	F	TOT.	N	W	M	F	TOT.	N	W	M	F	TOT.	N	W	M	F	TOT.	N	W	M	F	TOT.
0-999	Prem.	6	0	1	5	6	2	1	1	2	3	3	0	2	1	3	0	0	0	0	0	11	1	4	8	12
	Still.	1	1	1	1	2	0	0	0	0	0	1	0	1	0	1	1	0	1	0	1	3	1	3	1	4
1,000-1,999	Prem.	10	1	6	5	11	12	1	4	9	13	11	1	7	5	12	0	0	0	0	0	33	3	17	19	36
	Still.	4	0	3	1	4	2	0	2	0	2	1	0	1	0	1	0	0	0	0	0	7	0	6	1	7
2,000-2,249	Prem.	8	3	5	6	11	3	3	1	5	6	11	3	4	10	14	2	0	1	1	2	24	9	11	22	33
	Still.	1	0	0	1	1	1	0	0	1	1	0	0	0	0	0	0	0	0	0	0	2	0	0	2	2
2,250-2,499*	Prem.	7	4	4	7	11	2	3	2	3	5	0	2	1	1	2	1	0	0	1	1	10	9	7	12	19
	Still.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2,500 +	Still.	1	1	1	1	2	2	0	1	1	2	2	2	3	1	4	0	0	0	0	0	5	3	5	3	8
All weights	Prem.	31	8	16	23	39	19	8	8	19	27	25	6	14	17	31	3	0	1	2	3	78	22	39	61	100
	Still.	7	2	5	4	9	5	0	3	2	5	4	2	5	1	6	1	0	1	0	1	17	4	7	14	21

*2,250-2,349 grams for Negro babies, 2,250-2,499 grams for white babies.
N = Negro; W = White; M = Male; F = Female; Tot. = Total.

Table II presents the A-B-O typing data on 100 premature living infants and 21 stillborn infants, in relation to birth weight, sex, and color. In Table III the observed blood group frequencies in premature and stillborn infants are compared with those in the full-term controls.

The outstanding fact that can be seen from these tables is that group B forms 31 per cent of the premature series and 28.6 per cent of the stillbirth series, but only 22.5 per cent of the full-term babies. Chi-square of the differences between the control and premature series was 3.20 for all four blood groups. This is not significant at the 5 per cent level. However, if a fourfold comparison is made between groups O and B in the controls and in the premature infants, X^2 is 4.36, which is significant at the 5 per cent level. This is true because the effect on the X^2 of the stationary frequencies of groups A and AB is eliminated by a two-by-two comparison. If a test of the significance of differences is applied to group B, using groups B and O as the total population, significance at the 5 per cent level is again demonstrated ($t = 1.99$).

TABLE III. THE DISTRIBUTION OF THE A-B-O BLOOD GROUPS IN 1,154 TERM, PREMATURE, AND STILLBORN INFANTS

CLASS	BLOOD GROUPS								X^2 FOR THE COMPARISON OF GROUPS			
	O		A		B		AB		O-A-B-AB DF = 3	O-A DF = 1	O-B DF = 1	O-AB DF = 1
	N	%	N	%	N	%	N	%				
Full-term N = 1,033	492	47.6	266	25.8	232	22.5	43	4.2	CONTROLS			
Premature N = 100	39	39.0	27	27.0	31	31.0	3	3.0	5.10 $p > .10$	0.90 $p > .10$	4.36 $p < .05$	0.04 $p > .10$
Stillborn N = 21	9	42.9	5	23.8	6	28.6	1	4.8	–	–	–	–
Premature and stillborn N = 121	48	39.7	32	26.4	37	30.6	4	3.3	5.39 $p > .10$	0.57 $p > .10$	4.52 $p < .05$	0.09 $p > .10$

N = Number of individuals.

The stillbirth series is too small and incomplete to be of much value in comparison, although here too there was a trend toward a greater frequency of group B. The premature and stillbirth series combined for comparison with the controls gave X^2 of 5.39 for all four classes ($.10 < p < .20$), and one of 4.51 ($.02 < p < .05$) for groups O and B.

Four infants who died neonatally were tested, of whom 3 belonged to group B and one to group O. No comment can be made on this series, owing to its incompleteness.

The results also suggest a relationship between prematurity and sex (Table IV). Sixty-one per cent of the premature infants were female, while the full-term population showed the usual male predominance (51.92 per cent males). The difference in sex distribution between these two series was significant at the 5 per cent level ($X^2 = 6.33$). In order to further confirm this relationship, the records of the premature nursery for a 3½-year period prior to the commencement of this study were reviewed. From July, 1953, to November, 1956, 675 premature babies were born, of which 53 48 per cent were female. This sex distribution was also significantly different from the control series ($X^2 = 4.81$).

TABLE IV. THE SEX DISTRIBUTION OF 1,033 FULL-TERM INFANTS BORN FROM JANUARY THROUGH MAY, 1957, COMPARED WITH THE SEX DISTRIBUTION IN TWO SERIES OF PREMATURE INFANTS

CLASS	MALES		FEMALES		X^2
	N	%	N	%	DF = 1
Full-term N = 1,033	553	51.9	512	48.1	Controls
Premature January-May, 1957 N = 100	39	39.0	61	61.0	6.33 $p < .05$
Premature July, 1953-November, 1956 N = 675	314	46.5	361	53.5	4.83 $p < .05$

N = Number of individuals.

DISCUSSION

The incidence of the A-B-O groups in the series of full-term infants typed by us was not significantly different from the incidence of these groups in a series of pregnant women typed by the hospital blood bank (Table I). This is taken as evidence for the validity of our control figures.

The incidence of prematurity in the study population was 8.71 per cent of living births (102/1,171), as compared with the 8.49 per cent reported by Brown and associates[17] in a series of over 5,000 Negro infants, using the same criteria of prematurity.

The results of this study seem to show that there is a greater incidence of group B in the premature infants than one would expect by chance. Racial stratification (group B is more frequent in Negroes than in white) was not the cause of the difference, since only 78 per cent of the premature infants were Negroes, as compared to 83 per cent of the term babies.

The small stillbirth series also showed a trend toward an elevated frequency of group B.

It will be obvious that in studies of this type, large groups and high significances are necessary before much certainty may be attached to blood group relationships. If, however, there is a true association between group B and prematurity (or stillbirth), a potent mechanism for the reduction of the frequency of gene B would then exist. The premature population suffers a high mortality, and if premature infants of each group die at an equal rate, the total infant population at 1 month of age, for instance, would contain fewer B's than the total infant population at birth. This would be true because more of the B's are "at risk" as premature infants than would be expected if the premature births were randomly distributed among the four major blood groups. It is of interest to note that 17 of our 100 premature infants died, among whom were 6 O's, 5 A's, and 6 B's.

That there is a higher incidence of the female sex in premature infants seems clear, and has been reported before.[22] Although this fact would seem to favor the survival of the male sex, investigation of the sex-specific mortality rate revealed quite another situation. Eleven of the 17 deaths in the current series of 100 premature infants were in males. In the earlier series of 675 premature infants, 177 deaths occurred, of which 99 were in males and 78 in females. The mortality rate for premature males was thus 314.4 per thousand, while the rate for premature females was only 199.1 per thousand. Thus females survive prematurity better than males, although they suffer from the disease more often.

To the author's knowledge, there are no other papers with which one can compare the present findings. Polayes and associates[23] and Boorman[24] studied the blood types of newborn infants but did not distinguish between premature and full-term infants.

The present writer earnestly hopes that larger series of premature infants will be investigated to determine whether the higher incidence of group B herein reported is a true association or merely a statistical mirage.

CONCLUSIONS

1. In a comparison of the blood types of 100 premature and 1,033 full-term infants all born during a five-month period, there was a significantly higher incidence of group B in the premature series.

2. A small group of stillbirths showed the same trend.

3. The percentage of females in a previous series of 675 premature births and in the contemporaneous series of 100 premature infants was significantly higher than in the term babies.

4. The mortality rate for males born prematurely was much higher than for females.

5. If the relationship between blood group B and prematurity is substantiated, this might explain the relative infrequency of gene B in the western world.

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OBSERVATIONS ON THE PLASMA LIPOPROTEINS IN A CASE OF TAY-SACHS DISEASE

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FOR a number of years abnormalities in lipid metabolism have been suspected in Tay-Sachs disease, Gaucher's disease, and Niemann-Pick disease. The earliest studies in which these syndromes were described from clinical and pathological observations revealed large quantities of lipid deposited in various tissues.

More definite knowledge of the nature of the lipid or lipids involved and their origins has been obtained recently. In 1947, Klenk[1] demonstrated the presence of neuraminic acid in the lipid found in Tay-Sachs disease. This substance has been reported to occur normally in small amounts in cerebral tissue.[2] Schaffer[3] believed that the lipid originated in the brain itself as a result of a degenerative process of the ectoderm, while Bielschowsky[4] believed the Tay-Sachs syndrome to be the result of a defect in lipid metabolism, with the change in nervous tissue a secondary one. Sobotka and coworkers[5] presented the theory that an enzyme deficiency was involved.

Quite recently, Uzman[6] prepared a lipoprotein from splenic tissue obtained from patients with Gaucher's disease, and plasma and serum lipid values have been presented by Van Creveld[2] and Saifer.[7]

The purpose of this report is to present data on the plasma lipoproteins in a child with Tay-Sachs disease prior and subsequent to the use of a special diet. It is hoped that these data will stimulate further interest regarding the nature of the lipid disturbances in the lipoidoses.

CASE REPORT

N. G., a white female of Jewish parentage, was born on Sept. 4, 1955. The mother and father were not related by blood and their respective families came from widely separated parts of Poland and Russia. One male sibling, aged 8 years, is living and well, but had celiac disease as an infant. The next child, a male, had Tay-Sachs disease and died of pneumonia at the age of 22 months. The patient's birth weight was 9 pounds 12 ounces and she was thought to have a mild calcium deficiency neonatally. Calcium was administered orally up to the third week of life. At the age of 3 months, although she appeared to be developing normally, an ophthalmologist, consulted because of the family history, noted the presence of bilateral cherry-red spots in both macular areas. She was admitted to the Pediatric Service of Memorial Center for Cancer and Allied Diseases at the age of 6 months for observation.

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Physical Examination.—Examination showed a plump, contented though apathetic baby weighing 19 pounds. The temperature, pulse, and respirations were normal. She was unable to sit or pull herself up and grasped weakly at objects. The reflexes were hyperactive. The cherry-red spots were observed in both fundi. Although she had some vision, it was considered to be impaired.

Clinical Laboratory Findings.—A roentgenogram of the lungs was normal, but the thymic shadow was enlarged to the right. The urinalysis was normal. The hemogram showed hemoglobin, 12.6; white blood cells, 12.7, filamented neutrophils 21, lymphocytes 71 (2 atypical), monocytes 7, eosinophils 1. The total serum protein was 7.3 Gm. per cent, albumin 5.6 Gm. per cent.

Special Laboratory Methods and Findings.—The patient had a light breakfast of applesauce, but no fat-containing foods. At about 11:40 A.M., blood was withdrawn by femoral puncture. Exactly 25 ml. was transferred directly to a cold, calibrated cylinder containing 4 ml. of acid citrate dextrose (A.C.D.). Approximately 5 ml. of blood was transferred to a dry centrifuge tube containing about 1 mg. of heparin powder. Aliquots from each of these plasmas were analyzed for total nitrogen to determine the dilution of the plasma by the A.C.D.

The plasma was chemically fractionated into the alpha- and beta-lipoproteins according to Cohn's Method 10 as modified by Lever and associates.[8] The beta fraction was separated further in the preparative ultracentrifuge into lipoproteins of densities greater and less than 1.064 Gm. per milliliter.[9] Cholesterol and phospholipid were measured on the plasma and all the fractions to indicate the concentrations of lipoproteins present. The amounts of the S_f classes 0-10, 11-20, 21-100, and 101-400 in the low-density beta-lipoprotein fraction were calculated from the analytical ultracentrifuge data. A complete description of the methods has been published.[10]

The plasmas from two other children, aged 7 months, were studied as controls. One child had been hospitalized for a circumcision, the other for a congenital hip dislocation. These children were considered adequate for normal controls.*

In Table I are the plasma lipoprotein data obtained from the patient and the mean values from the control subjects. Although the patient had greater quantities of both cholesterol and phospholipid in the plasma, the most striking differences were in the low-density beta-lipoprotein fraction, and S_f classes, which were present in notably greater concentrations than observed in the normal subjects.

As a result of these differences, and in cognizance of the characteristics of the syndrome and the usual postmortem findings, a dietary regimen was devised (Table II). This diet was designed to provide the following: (1) good nutrition for a growing baby in that the requirements for protein, carbohydrates, vitamins, mineral, essential fatty acids, bulk, and calories were met; (2) the fat as vegetable fat; (3) the essential unsaturated fatty acids; (4) in particular, a good source of choline and/or methionine; (5) a diet acceptable to the child.

The subject was on the diet for four and one-half months, at which time another blood sample was analyzed.

In the third column of Table I are the plasma lipoprotein data obtained after the period of controlled food intake. In addition to lower quantities of both cholesterol and phospholipid in the whole plasma, there were decreases in the low-density beta-lipoprotein fraction and in all the S_f classes studied. The quantity of S_f 0-10 class was reduced 48.6 per cent; S_f 11-20, 24 per cent; S_f 21-100, 60.6 per cent, and S_f 101-400, 100 per cent.

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*The authors are very grateful to Dr. Fred Eagle, St. Luke's Hospital, New York, for making the control subjects available.

TABLE I. THE PLASMA LIPOPROTEINS IN A BABY WITH TAY-SACHS DISEASE, BEFORE AND AFTER A CONTROLLED DIET, AND COMPARED WITH CONTROL BABIES

COMPONENT MEASURED	TAY-SACHS DISEASE 2/15/56 (AGE, 5 MO.)		CONTROL BABIES (AGE, 7 MO.)		TAY-SACHS DISEASE 6/27/56 (AGE, 9.5 MO.)	
	MG. %	% OF TOTAL	MG. %	% OF TOTAL	MG. %	% OF TOTAL
Cholesterol						
Plasma	248		223		152	
Alpha-Lipoprotein	42	17	41	18	35	23
Beta-Lipoprotein	197	79	183	83	111	73
Low-density Beta-Lipoprotein	176		144		98	
S_f 0-10	452		414		232	
S_f 11-20	33		13		25	
S_f 21-100	61		10		24	
S_f 101-400	6		0		0	
High-density Beta-Lipoprotein	20		20		15	
Phospholipid						
Plasma	251		215		196	
Alpha-Lipoprotein	86	34	98	46	76	39
Beta-Lipoprotein	154	61	113	52	98	50
Low-density Beta-Lipoprotein	129		83		52	
High-density Beta-Lipoprotein	17		23		29	

TABLE II. DIETARY REGIMEN

DIETARY CONSTITUENT	TOTAL GRAMS	COMPOSITION IN GRAMS			TOTAL CALORIES
		PROTEIN	FAT	CARBOHYDRATE	
Soybean milk–Mull-Soy (mixed)	930.0	27.8	37.2	41.8	620
Cereal-Pablum	74.0	10.1	2.2	50.0	262
Liver	5.0	1.0	0.5	0.2	10
Banana	50.0	0.5	0.1	11.0	65
Cottonseed oil	10.0	0.0	10.0	0.0	93
Prunes	120.0	0.9	0.2	28.9	119
Essential B vitamins-Vi-Penta	0.3	0.0	0.0	0.0	0
Cevex	0.6	0.0	0.0	0.0	0
Orange juice	90.0	0.0	0.0	10.0	41
Total composition in grams		40.3	50.2	141.9	
Calories from protein, fat, and carbohydrate		161.1	466.9	581.8	
Total calories					1,210
Per cent calories from protein, fat, and carbohydrate		13.0	39.0	48.0	

When the postdietary plasma lipid and lipoprotein values from the patient are compared with the control values, it may be seen that all components, *except* the S_f classes 11-20 and 21-100, are appreciably lower. The values for these two most important S_f classes were decreased following the special diet, but continued to remain well above the values for normal babies.

Clinical Course.—From the date she was first observed by us her course was one of slow general decline. She showed reduced motor activity and diminishing attempts to focus her eyes. She ate satisfactorily, except for the liver, which was not well accepted. At 9½ months her lipoproteins were again studied (Table I) and similar tests were made on her parents (Table III). Her weight at 1 year of age was 22

TABLE III. PLASMA LIPOPROTEINS IN THE PARENTS OF THE PATIENT WITH TAY-SACHS DISEASE COMPARED WITH NORMAL WOMEN AND MEN IN ABOUT THE SAME AGE GROUP

COMPONENT MEASURED	MOTHER OF PATIENT		MEANS OF NORMAL WOMEN		FATHER OF PATIENT		MEANS OF NORMAL MEN*	
	MG. %	% OF TOTAL	MG. %	% OF TOTAL	MG. %	% OF TOTAL	MG. %	% OF TOTAL
Cholesterol								
Plasma	257		208		233		197	
Alpha-Lipoprotein	57	22	55	27	51	22	50	25
Beta-Lipoprotein	206	80	145	70	174	75	142	72
Low-density Beta-Lipoprotein	154		114		137			
S_f 0-10	396		260		328			
S_f 11-20	34		26		42			
S_f 21-100	60		29		46			
S_f 101-400	0		0		11			
High-density Beta-Lipoprotein	27		21		16			
Phospholipid								
Plasma	251		241		226		195	
Alpha-Lipoprotein	100	40	122	50	103	46	83	42
Beta-Lipoprotein	131	52	117	49	124	55	87	45
Low-density Beta-Lipoprotein	95		83		97			
High-density Beta-Lipoprotein	33		25		18			

*Calculated from data in reference 12.

pounds 10 ounces. At 15 months of age she developed acute tracheobronchitis and was hospitalized again for 18 days. Recovery from this was uneventful but she became progressively weaker and expired at the age of 21 months.

Family History, and Plasma Lipoproteins From the Parents.—As cited above, the parents know of no contributory causes in their families, but one of the patient's siblings had evidences of a lipid metabolism disorder. Consequently, the plasmas from the patient's parents were studied by the same procedures. The results are in Table III, along with the mean values for the same components obtained from 24 normal young women.[11] The available comparable data for men are given.[12] The mother has greater quantities of the S_f classes, especially 21-100, and lower quantities of alpha-lipoprotein phospholipid than the normal women. Compared with the available data for normal men, the father has slightly greater quantities of whole plasma and beta-lipoprotein cholesterol and phospholipid. With the exception of the elevated value for S_f class 21-100, it should be concluded that the plasma lipoprotein values found in the patient's parents are within the normal ranges, and afford no substantial contributory information.

DISCUSSION

The findings of various investigators[13, 14] have shown that changes in blood cholesterol levels occur with a change of the ingested fats from those of animal origin to those of vegetable origin. Some of these experiments have concerned abnormal human beings and others were conducted on animals. Kinsell and co-workers[15-17] found a considerable reduction in the serum cholesterol and phospholipid levels in patients fed on a high vegetable fat diet. Ahrens and associates[18] demonstrated in six patients that significant reductions in free and esterified cholesterol and phospholipid levels in the serum were obtained when plant fats were substituted isocalorically for animal fats.

The fats in the diet of most human infants, during the first six months of life at least, are largely of animal origin. The metabolic defect in the lipoidoses may be related to the improper utilization of an unacceptable lipid or to deficiencies which in some way prevent the correct assimilation of fats suitable for normal infants. Such deficiencies might be choline and/or methionine[19] or the essential fatty acids.[20] If this is so, it is conceivable that dietary alterations instituted during early life might prevent the inevitable fatal outcome.

In our patient the disease was clinically established prior to the alteration of the diet from animal to vegetable fat, and the inclusion of the essential fatty acids and methionine and/or choline.

Despite the progression of disease, the patient maintained at least an average state of nutrition and skeletal growth, and when the postdietary lipoproteins were studied, the high values previously found had decreased. It may be significant that most of the postdietary lipoprotein values fell far below those of the normal babies who were on the usual infant formula. The continued high quantities of the S_f classes 11-20 and 21-100 may indicate that there is some derangement in lipid metabolism. Should these findings be confirmed, a possible avenue of correcting a metabolic disorder might be indicated.

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Practical Value of Higher Mathematics

March 23, 1787. A child of Mr. David Scovil of Merriden being three years and five months old, was troubled with worms, the mother gave it something to fetch them away, and in about 12 days came away 40, and then the child was taken in extreme pain, which brought on a fever, a physician was sent for and by the means that was given in the compass of seven days 230 worms more came from the child, at least six inches long upon the average, which, together with the 40 that came before, made 270, reckoning the whole at 6 inches each, would make it equal to one 1620 inches long or 135 feet, which would be at least 34 times the length of the child.

Cumberland Gazette. March 23, 1787.

ADDISON'S DISEASE IN CHILDREN

Report of Two Cases

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Chronic adrenal insufficiency (Addison's disease) is a rare condition in the pediatric age group. This is especially true regarding those cases of primary adrenal atrophy or involution, not associated with adrenal destruction by disease processes or hemorrhage, or specific abnormality in hormone synthesis. Snelling and Erb[1] reported the first case of primary adrenal atrophy in the pediatric literature in 1935, a 9½-year-old boy. In a review of the literature up to 1946, Jaudon[2] summarized all reported cases of Addison's disease in children under 15 years of age in which autopsies had been done. Of this group of 59 cases, only 12 patients were less than 10 years of age; adrenal atrophy was encountered in only 6 cases, while 53 cases demonstrated destruction of the adrenals by tuberculosis. Talbot, Sobel, McArthur, and Crawford[3] reviewed their experiences up to 1952, based on nine cases over a 15-year period; no cause for the chronic adrenal insufficiency could be found in five of these cases. In infancy, chronic hypoadrenalism, except for that related to the metabolic variations in patients with congenital adrenal hyperplasia, is an almost unrecognized entity, according to Geppert and associates.[4] The relative incidence of primary adrenal atrophy or idiopathic cytotoxic adrenal necrosis as causes of Addison's disease has markedly increased in the last ten years, largely because of the general reduction and more successful handling of tuberculosis[2, 3, 5, 6]; accordingly, it appears that the true clinical incidence of Addison's disease in all age groups has been reduced, as compared with previous experience.

We are reporting two cases where the usual clinical and laboratory data had to be supplemented by measurements of adrenal hormones in urine and blood before a well-established diagnosis of Addison's disease could be made.

CASE REPORTS

Case 1.—M. S., an 11-year-old white boy, was first seen in the outpatient department of Children's Hospital of Michigan during July, 1955, because of the development of persistent vomiting followed by dehydration and disorientation of two days' duration. He had a previous episode of marked dehydration and disorientation after a sore throat in July, 1954. Following a tonsillectomy and adenoidectomy in December, 1954, he had a similar episode of lethargy and semicoma that lasted 48 hours. For the year preceding his initial clinic visit, his parents noted increasing lethargy, fatigability, irritability, and diminished school performance. Careful family history was completely negative. Past history revealed a normal growth and development until the age of 7 to 8

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years, except for enuresis throughout most of his life, which had persisted unchanged. He had no significant diseases prior to the present illness.

Physical examination revealed a small, poorly developed, poorly nourished boy, falling below the grid in height and weight. Scattered nevi and diffuse tan pigmentation were present over extremities, with no mucosal, nipple, or palmar accentuation. Blood pressure was 90/60, weight 50 pounds, height 51 inches. Head to pubis measured 21 inches, arm span 49 inches. The remainder of the examination, including fundoscopic and neurological, was entirely negative.

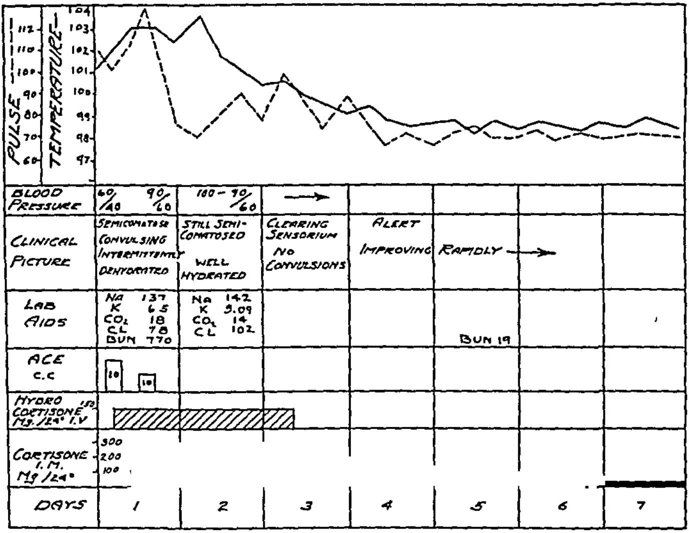

Fig. 1.—Case 1. The clinical and therapeutic course of an acute salt-losing adrenal crisis.

Diagnostic studies included the following: (1) Bone age was four years behind his chronological age; the bone survey, including skull films, was otherwise normal. (2) An electroencephalogram, taken in repose and light sleep, had frequencies at the low end of the normal range but no abnormal wave forms and was considered to be within normal range (Dr. A. J. Derbyshire). (3) Extensive laboratory studies revealed only the following points of interest: serum CO_2, 26 mEq./L.; serum Cl^-, 99 mEq./L.; serum Na, 148 mEq./L.; serum K, 5.2 mEq./L.; PBI, 6.5 mcg. per cent; circulating eosinophil count, 66/c.c. (4) Insulin tolerance test was as follows: fasting blood sugar, 82 mg. per cent; 20 min., 24 mg. per cent; 40 min., 33 mg. per cent; 60 min., 32 mg. per cent; 90 min., 34 mg. per cent; with a normal response to epinephrine. (The patient experienced no adverse symptoms during this procedure.)

After several months of observation, the child was placed on methyl testosterone, 5 mg. daily, on alternating weeks for 3 months, but showed no significant anabolic response or change in bone age. Likewise, no development of secondary sex characteristics ensued.

Admission to the hospital on Feb. 12, 1956, was prompted by fever and sore throat followed by rapidly developing lethargy, vomiting, and semicoma. At this time, history revealed an excessive salt intake for the preceding six months.

Physical examination revealed a semicomatose underdeveloped boy in acute distress. Blood pressure was 60/40, pulse 140, respirations 44, temperature 101° F. Pigmentation was present, as previously noted in the outpatient department. Bilateral otitis media and acute pharyngitis existed. Otherwise there were no new findings.

A clinical diagnosis of acute adrenal insufficiency was made, and he was treated with saline, aqueous adrenal cortical extract (ACE), and hydrocortisone intravenously and cortisone acetate intramuscularly, as outlined in Fig. 1. The response was dramatic, with almost an immediate clinical improvement following this therapy.

At this time, the diagnosis of chronic adrenal insufficiency was recognized; the exact nature of it remained to be clarified. Accordingly, the patient was discharged on no adrenal steroids but on supplemental salt to await time for appropriate studies. At the time of discharge all serum chemistries had returned to normal. Likewise, an intradermal skin test with OT 1:4,000 was negative, as was a histoplasmin skin test. A flat plate of the abdomen revealed no adrenal calcifications.

The patient was readmitted three weeks after discharge for diagnostic purposes and was given ACTH intravenously, 25 units daily over an 8-hour period for 3 days, followed by ACTH gel intramuscularly, 20 units daily for 10 days. The results of these studies, as reflected by eosinophil counts and urinary 17-ketosteroids, are recorded in Table I. There was no significant change in his circulating eosinophil count, his urinary 17-ketosteroids, which were 0.7 and 1.3 mg. per day as base-line values, or his urinary uric acid : creatinine ratio, determined before and after the first ACTH infusion. During the period of intravenous ACTH, although receiving 10 Gm. of oral sodium chloride daily, his serum sodium fell to 126 mEq./L. and his serum chloride fell to 72 mEq./L., requiring intravenous saline infusions to correct the deficit.

He was then considered to have primary Addison's disease, due to idiopathic atrophy or involution of the adrenal glands. Accordingly, he was placed on cortisone acetate, 5.75 mg. twice a day orally, and 9-alpha-fluorohydrocortisone (Florinef) 0.15 mg. daily.

Since being placed on the above regimen, he has had no recurrence of previous symptoms; during these past 16 months, he has exhibited a 22 pound weight gain, a 2½ inch increase in height, and a marked increase in exercise tolerance and over-all interest in his surroundings. He has had two episodes of pharyngitis which were easily tolerated with increases in cortisone dosage to 50 mg. per day for a 2- to 3-day period. Serum sodium and potassium levels have been determined

TABLE I. THE RESPONSE OF CASE 1 TO 25 UNITS AQUEOUS ACTH INTRAVENOUSLY OVER AN 8-HOUR PERIOD FOR THREE DAYS, FOLLOWED BY 20 UNITS ACTH GEL INTRAMUSCULARLY DAILY FOR 10 DAYS, AS JUDGED BY URINARY 17-KETOSTEROID LEVELS AND CIRCULATING EOSINOPHIL COUNTS

DAY		CONTROL	1	2	3	13
Eosinophil count (number per cubic centimeter)	9 A.M.	240	300	275	210	
	3 P.M.	250	375	325	172	
Urinary ketosteroids (milligrams per 24 hours)		1.07	1.02	1.0	1.3	1.2
ACTH units USP (intravenous every 8 hours)			25	25	25	
ACTH units USP (intramuscular)						20 Day 4-13

at two-month intervals, and have remained within normal limits. 9-alpha-fluorohydrocortisone was reduced to 0.1 mg. daily after six months because of a slight increase in diastolic pressure.

CASE 2.—B. W., a 7½-year-old white boy, was entirely well until 3 years of age, when he was admitted to another hospital because of high fever, repeated episodes of vomiting, and lethargy. He improved on symptomatic therapy only and was discharged after a few days. However, following hospitalization, periodic episodes of fever and easy fatigability occurred at approximately monthly intervals. Diffuse darkening of skin color was noted to develop slowly during this period, with a change in hair color from blond to dark brown.

At the age of 4 years he began to have episodes of fever, vomiting, and delirium at more frequent intervals. During one such episode, he was studied at another institution, where hepatosplenomegaly was noted. During hospitalization, he had fever, convulsions, and an "encephalitis-like" picture, associated with periodic gray cyanosis and severe prostration. No definite diagnosis was made at that time. One month later, at the same institution, tonsillectomy and adenoidectomy were performed without adverse reaction.

At the age of 5¼ years, he was transferred to this hospital with a history of fever, vomiting, and abdominal pain for 8 days, and the development of a comatose state 24 hours before admission. While at the transferring institution, on the day of admission to this hospital, a blood sugar level (Folin-Wu method) too low to be recorded and a marked lowering of the serum CO_2 content were found.

On admission, he was a diffusely pigmented, fairly well-developed and well-hydrated, normotensive white male, weighing 45 pounds. He was in a comatose state, responding to painful stimuli only. On the basis of a provisional diagnosis of adrenal insufficiency, steroid therapy was initiated with cortisone acetate, 200 mg. daily intramuscularly, along with continuous intravenous fluids and tube feedings. At the end of 20 days of this treatment, his sensorium had improved to the point of responding to simple commands and accepting oral nourishment. At this time, steroids were discontinued. Within 72 hours, however, he presented a picture similar to that on admission and was replaced on cortisone, which was eventually discontinued on the sixtieth hospital day after a gradual reduction during the preceding week.

Laboratory evaluation during this admission revealed the following significant points: urinalyses were normal; urinary amino acid N excretion was normal; normal blood sugar levels were persistently found; serum electrolytes were never significantly abnormal, although the serum K tended to be between 5 and 6 mEq./L.; spinal fluid was normal, including protein; skin biopsy revealed only excessive melanin pigmentation in germinal epithelium; skin tests with OT were repeatedly negative; eosinophil counts varied considerably, irrespective of clinical and therapeutic state; electroencephalogram was interpreted as showing a nonspecific state of delirium (Dr. A. J. Derbyshire); x-rays revealed a normal skull and normal-sized heart.

At the conclusion of this hospitalization (total duration of 78 days), with the patient appearing to be entirely normal except for his pigmentation, no definitive diagnosis was established. It was felt that the child had responded favorably to steroid therapy but had exhibited no untoward effects during and after ultimate withdrawal.

At 5¾ years of age, he was admitted again with the history of fever, vomiting, and disorientation, and, immediately prior to admission, tarry stools. He was not in acute distress during initial examination, although he was moderately dehydrated and had an acute pharyngotonsillitis. His weight was 46 pounds, pulse 140, respirations 30, and temperature 100.6° F. His clinical course was relatively benign, with a rapid return of a normal sensorium on intravenous fluids alone.

Laboratory studies at this time revealed the following: CO_2, 13 mEq./L.; Cl^-, 109 mEq./L.; pH 7.29; total base 148 mEq./L.; normal 4-hour oral glucose tolerance test. A Thorn test showed a greater than 50 per cent drop in circulating eosinophil count following ACTH.

Serum chemistries drawn before therapy was initiated revealed the following: blood sugar, 50 mg. per cent; serum CO_2, 16.5 mEq./L.; serum Cl^-, 100 mEq./L.; serum Na, 143 mEq./L.; serum K, 4.13 mEq./L. He was again placed only on intravenous fluids and his subsequent course was uneventful, with a total hospitalization of three days.

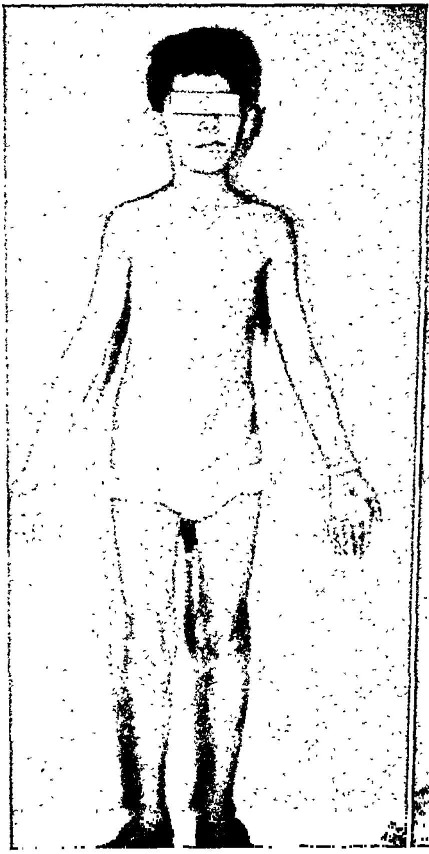

Fig. 2.

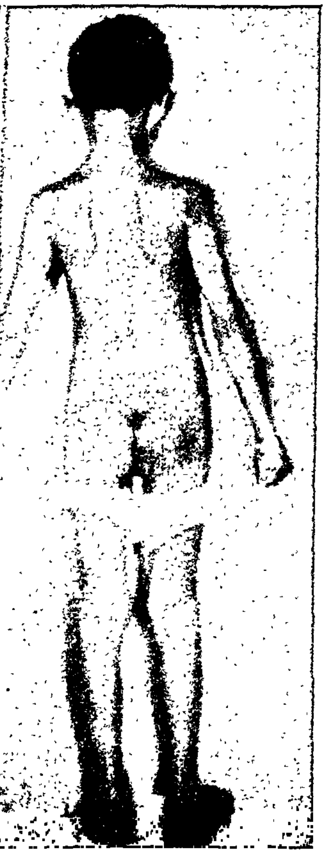

Fig. 3.

Fig. 2.—Case 2. Anterior full-length view, showing over-all increased pigmentation.

Fig. 3.—Case 2. Posterior full-length view, demonstrating increased pigmentation of elbows, lumbosacral area.

At 6¼ years of age, he was again admitted because of vomiting, weakness, fever, dehydration, and the development of a semicomatose state. Blood pressure was 110/75, pulse 120, respirations 30, temperature 102° F.

At home he did relatively well except for a persistence of easy fatigability, awkward and incoordinate gait exacerbated by exercise, and only fair school performance, thought to be due to fatigue and inattention.

At 7¼ years of age (March 3, 1957), his admission was precipitated by fever, vomiting, and, again, disorientation. Physical examination revealed a disoriented boy with an increase in over-all pigmentation, accentuated in skin creases and scars. There was also marked oral mucosal pigmentation, and the patient was markedly dehydrated. Blood pressure was 80/60, pulse 140, respirations, 28, temperature 100° F. Figs. 2-5 depict the marked pigmentation and general appearance of the patient at this time.

Serum chemistries before the initiation of therapy were as follows: blood sugar (venous) 9 mg. per cent; CO_2, 14.5 mEq./L.; Cl^-, 88.6 mEq./L.; Na, 140 mEq./L.; K, 5.0 mEq./L.; Ca, 10.4 mg. per cent; P, 4.9 mg. per cent; blood urea nitrogen, 26 mg. per cent. Subsequent chemistries were within normal limits.

At this point, a diagnosis of Addison's disease was entertained, and the following studies were performed:

1. OT 1:4,000 and 1:100 skin tests were negative. Histoplasmin skin test was negative.

2. Studies of the patient's carbohydrate metabolism were made, as shown in Fig. 6. Insulin tolerance test demonstrated increased sensitivity to insulin, but no untoward reactions were experienced. (A continuous saline intravenous infusion was kept running during the course of the insulin tolerance test to allow immediate administration of hypertonic glucose if necessary.) The intravenous glucose tolerance curve was normal, followed by a normal response to adrenalin. A 5-hour oral glucose tolerance test produced abnormally high and prolonged elevation of blood sugar levels, without a fasting or late hypoglycemia.

3. Chest film showed a normal-sized heart. A flat plate of the abdomen demonstrated no adrenal calcifications. Films of long bones revealed a normal mineral content and normal bone age.

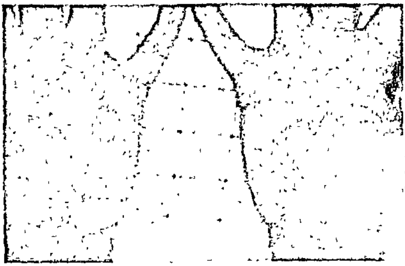

Fig. 4.

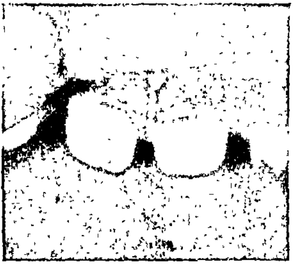

Fig. 5.

Fig. 4.—Case 2. Increased pigmentation in skin creases.

Fig. 5.—Case 2. Marked deposition of pigment at gingival margin and scattered over tongue

4. Electroencephalographic studies demonstrated a No. 3 borderline abnormal tracing (on a scale of 1 to 5) with some asymmetric bursts in sleep, strongest in the left frontal and temporal area. (Dr. A. J. Derbyshire.)

5. Robinson-Power-Kepler water test revealed a normal response to a water load, and the factor A was 72 (normal).

6. ACTH, 80 units, was given intravenously over an 8-hour period daily for five consecutive days. Urinary 17-ketosteroids, urinary 17-hydroxycorticoids, urinary creatinine levels, and circulating eosinophil counts were determined, as recorded in Fig. 7. No significant response to ACTH occurred.

7. Two days after the conclusion of the above, plasma 17-hydroxycorticoid levels were determined before and 4 hours after the administration of 80 units ACTH gel intramuscularly, with the finding of *no demonstrable levels* either before or after ACTH.

On the basis of these studies, it was concluded that the patient failed to respond normally to the stimulus of ACTH. Along with the history and corollary physical findings, the diagnosis of Addison's disease, due to adrenal atrophy or involution, was

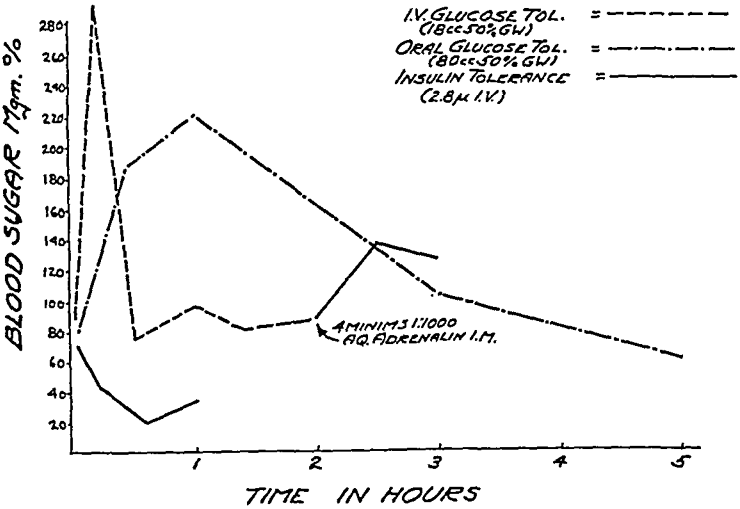

Fig. 6.—Case 2. Tests of the patient's carbohydrate metabolism during his last hospital admission, aged 7¼ years.

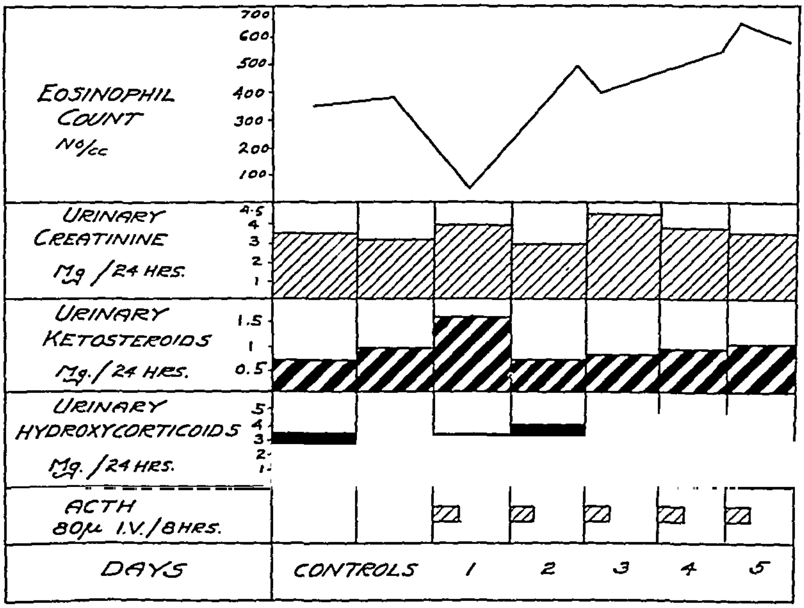

Fig. 7.—Case 2. Response to 80 units aqueous ACTH administered intravenously over an 8-hour period for five consecutive days.

made. Treatment with cortisone, 12.5 mg. orally twice a day, was initiated, followed in two weeks with the addition of 9-alpha-fluorohydrocortisone, 0.1 mg. daily, because of persistence of excessive salt intake and inadequate over-all clinical response.

DISCUSSION

While patients with Addison's disease almost always have clinical or, at least, laboratory evidence of partial or complete lack of all three adrenocortical hormone types, deficiency in either glucocorticoids or mineralocorticoids tend to be individually prominent, especially as regards the presenting signs or symptoms. This is well exemplified by contrasting the two cases reported here. In Case 1 (M. S.), the diagnosis was eventually established with certainty following a typical adrenal crisis precipitated by an acute infection, manifested by severe dehydration, hemoconcentration, hypotension, and circulatory collapse, with serum electrolyte determinations reflecting salt loss and potassium retention. In Case 2 (B. W.), repeated episodes of both documented and probable hypoglycemia, preceded by vomiting, abdominal pain, and fever, occurred before the diagnosis was ultimately made. The importance of eliciting a history of excessive salt craving should be emphasized, especially with reference to Case 1 who, in retrospect, had been taking a markedly excessive amount of salt, even to the point of taking rock salt to bed with him at night. It is interesting to note that this history was missed even though the family carefully recorded every type and amount of food ingested by the patient over a two-week period, except salt. Both cases demonstrated pigmentation of varying degrees, with a typical appearance and distribution characterizing Case 2; that is, the diffuse dark-brown pigmentation was distributed over the entire body, being more marked on the nipples, elbows, low back, scars, and with extensive oral mucosal and tongue deposition as well. The prolonged duration before diagnosis in both cases, in the absence of any evidence of specific disease processes involving the adrenals, supports the concept of slow adrenal involution or atrophy that must occur in such situations, as opposed to the clinical course following acute cortical necrosis or vascular accidents which, by necessity, is usually much more precipitous and acute in onset. While the diagnosis, in retrospect, is easy and classical in both of the cases reported, it is important to note the difficulties that can be encountered unless the entity is carefully considered in any child reflecting the pattern of asthenia, anorexia, weight loss (or failure to gain adequately), recurrent dehydration and/or hypoglycemia and general debility, and unless appropriate and specific laboratory investigations are performed. The symptoms and signs of adrenocortical insufficiency seldom suffice to certify a diagnosis.[3]

Methods of Laboratory Diagnosis.—Laboratory aids, not involving the actual measurement of adrenocortical hormone levels in urine and blood, are based on indirect physiologic effects of adrenal products; as such, they are subject to a large number of variables, both clinical and laboratory, and, thus, tend often to be misleading. The oral glucose tolerance curve is usually flat, with a drop to hypoglycemic levels several hours after the administration of glucose; in both patients, repeated oral glucose tolerance tests reflected normal curves or, as in Case 2, even curves with marked and prolonged elevation of blood sugar from a normal fasting level. The injudicious use of the insulin tolerance test has been frequently warned against because of the marked increase in insulin sensitivity manifested in patients with adrenal insufficiency[3, 6]; in both of the cases reported, insulin tolerances were determined with intravenous saline running slowly to allow rapid administration of hypertonic glucose if necessary. In both cases, increased sensitivity was demonstrated to relatively small doses but no untoward reactions were experienced, even with blood sugar levels as low as 20 mg. per cent. The inability of a patient with adrenal insufficiency to produce diuresis in response to a water load is determined by the Robinson-Power-Kepler test[6]; in Case 2 a normal response to a water load was obtained. The failure to demonstrate hyponatremia (as in Case 1) and hypochloremia during an acute adrenal crisis is related to the over-all contraction of extracellular volume; accordingly, hyperkalemia is the only relatively consistent electrolyte aberration in acute adrenal insufficiency. The effect of ACTH on the circulating eosinophil count (Thorn test) has been used since 1948 as a test of adrenal reserve; in Case 2, a normal response (greater than 50 per cent drop in the circulating eosinophil count four hours after intramuscular administration of corticotrophin) was obtained during his second admission to this hospital at the age of 5¾ years. Thus, while of considerable help, the tests mentioned above have severe limitations, as exemplified in both cases reported, and may obscure an underlying adrenal insufficiency by false negative results unless the recent advances in laboratory diagnosis of Addison's disease are utilized.

The use of ACTH as a means of estimating the ability of the adrenal gland to respond has been given great impetus by the development of relatively simple determinations of corticosteroid excretions in blood and urine, and it is now felt that the determination of 17-hydroxycorticoids and 17-ketosteroids in blood and urine provides the most accurate practical means of quantitating adrenocortical response.[7-9] Several conclusions can be drawn from the recent literature regarding urinary excretion studies following ACTH administration: (1) At least a three-day period should be used for study because of the initial delay in response that may occur in the presence of normal adrenals as well as in patients with inanition, anterior pituitary insufficiency, etc. (2) A significant increase is more commonly found when measuring urinary corticosteroids as compared to urinary 17-ketosteroids. (3) The use of both determinations, however, significantly increases the reliability of the test procedure. (4) In general, an increase of at least 100 per cent in the excretion of both 17-ketosteroids and 17-hydroxycorticoids has been found in all patients except those with primary adrenal disease, regardless of the route of administration of ACTH. However, as might be anticipated, due to the variety of factors that cannot be controlled in such a test situation, the value of ACTH stimulation lies mainly in the diagnosis of frank primary adrenal insufficiency and does not, as yet, allow more subtle estimations of the relative ability of an adrenal gland to respond. In both cases reported, complete absence of response after prolonged administration of ACTH is diagnostic of true adrenal insufficiency.

The measurement of plasma corticoids and their change in response to corticotropin has afforded an even more sensitive tool in the diagnosis of states of adrenal hypofunction. Utilizing their own method for the determination of plasma 17-hydroxycorticoids (normal plasma levels 5 to 10 mcg./100 ml.), Nelson and coworkers[10] found no measurable corticoid level in several patients with Addison's disease. When ACTH was given to normal persons, an increase in plasma level to a peak of 20 mcg./100 ml. was obtained; the peak was reached 60 minutes after intravenous dose, with a return to normal in four hours. When ACTH was given intramuscularly, the peak occurred in two hours, with a return to normal in six hours. Bayliss and Steinbeck[11] gave 80 units ACTH gel to normal patients, and demonstrated a rise of plasma hydroxycorticoid levels to 36 mcg./100 ml. in two hours, and a maximum concentration in four to eight hours, with a return to normal in 12 to 24 hours. Wallace and associates[12] found levels of 0 to 21 mcg./100 ml. in patients with Addison's disease; when two such patients were given ACTH, no rise occurred. They stressed the point that patients with Addison's disease may have normal circulating corticoid levels, but do not respond to ACTH. In our Case 2, no measurable levels were found before or four hours after administration of 80 units ACTH gel.

Treatment of Acute Adrenal Crisis.—The aims of treatment of the acute crisis are: (1) restoration of plasma and extracellular fluid volume, (2) correction of hypoglycemia, if present, and restoration of carbohydrate reserves, (3) treatment of the precipitating or complicating infection, and (4) replacement of absent or deficient circulating adrenocortical hormones.[13] Aqueous adrenal extract (ACE) is an extract of natural adrenocortical hormones obtained from the adrenals of domestic food animals; 1 c.c. of ACE is equal to 0.1 mg. hydrocortisone in activity. Yet, the life-preserving effects of ACE exceed that to be obtained from their content of corticosterone and 17-hydroxycorticosterone alone[3]; and thus, combined with the advantages of ease of administration, wide range of safety, and rapid action when given intravenously, the use of ACE is still advisable in the initial therapy of an acute crisis. Hydrocortisone sodium succinate (Solu-cortef) may be administered by an easily titratable intravenous drip in glucose-saline solutions, which makes its emergency use ideal in that dosage can be altered with the clinical changes of the patient. This would seem to be especially valuable since dosages are approximate, depend on the relation between adrenal reserve and the magnitude of the stress, and change with either improvement or deterioration of the patient. The use of desoxycorticosterone actetate (DCA) is necessary mainly in the presence of hyperkalemia, since hyponatremia and hypochloremia, and the correction of circulating blood volume, can and should be handled mainly by the use of intravenous sodium chloride-containing solutions. Maintenance therapy with cortisone or hydrocortisone by oral or intramuscular route is initiated later in the course of therapy when intravenous fluids (and thus intravenous hydrocortisone) are no longer necessary.

Recent Aspects of Maintenance Therapy.—In the replacement therapy of Addison's disease, it would be advantageous to be able to use agents that, with a minimum of expense and deleterious side effects and a maximum of stability, would provide oral replacement therapy in as physiologic a manner as possible. Cortisone, hydrocortisone, and their derivatives provide adequate glucorticoid properties but do not supply sufficient mineralocorticoid properties in the doses required for maintenance therapy. Use of supplemental salt and DCA parenterally (in the forms of acetate in oil, trimethylacetate, or pellets) has been necessary to create adequate mineral homeostasis. Substitution of a fluorine atom in the 9-alpha position of the hydrocortisone molecule produces a marked potentiation of glucocorticoid effect and an even greater potentiation of mineralocorticoid effect, so that 9-alphafluorohydrocortisone has a "salt activity" 50 times and a "sugar activity" 20 times that of hydrocortisone.[14, 15] The sodium-retaining properties of the fluorinated compound and aldosterone are comparable. Its use alone in replacement therapy of Addison's disease produces edema and hypertension in doses necessary to achieve adequate glucocorticoid effects. However, when used in small doses, together with cortisone or hydrocortisone, effective, safe, and relatively inexpensive oral therapy results. Leith and Beck[16] reported on 8 adult patients well handled with 0.1 mg. 9-alpha-fluorohydrocortisone and 5 mg. hydrocortisone twice daily. Kupperman and Epstein[17] reported similar success with combined therapy, as have Owen and associates[18] who pointed out the dangers involved in excessive dosage and the importance of individualization of therapy. Our patients are being successfully maintained on such combined therapy, with no significant difficulties experienced thus far.

SUMMARY

Two cases of primary chronic adrenal insufficiency (Addison's disease) in children are presented.

The symptoms and signs of chronic adrenocortical insufficiency seldom suffice to certify a diagnosis. Similarly, reliance on laboratory methods that *do not involve actual measurements of* adrenal hormones in plasma and urine may obscure an underlying adrenal insufficiency by false-negative results.

The use of the quantitative adrenal response to ACTH stimulation as reflected in urinary excretion of 17-ketosteroids and 17-hydroxycorticoids and plasma 17-hydroxycorticoid levels provides the most accurate laboratory tool now available in the diagnosis of Addison's disease.

The use of 9-alpha-fluorohydrocortisone provides an agent which, when used together with cortisone or hydrocortisone, promises to allow effective, safe, and relatively inexpensive oral therapy for chronic adrenal insufficiency.

Appendix of Methods.—(1) Blood sugars were done by Folin-Wu method. (2) Urinary creatinines were done by Folin method. (3) Urinary 17-ketosteroids were done by the Klendshoj modification of the Drekter method.[19] (4) Urinary 17-hydroxycorticoids were done by a modification of the Reddy procedure.[20] (5) Plasma 17-hydroxycorticoids were done by an adaptation of the method published by Silber and Bush.[21]

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SUCROSURIA IN ASSOCIATION WITH MENTAL DEFICIENCY AND HIATAL HERNIA

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SUCROSE is an assimilable disaccharide which is normally rapidly hydrolyzed in the intestines by the digestive enzymes to its constituent monosaccharides, glucose and fructose, which are then absorbed and utilized. Like other disaccharides, unless hydrolyzed it is not absorbed in appreciable quantities from the alimentary tracts of normal animals. If, however, it gains access to the body without having been broken down, it is almost entirely excreted in the urine without change. Apparently the digestive juices are the only enzymes in the body capable of hydrolyzing the polysaccharides to utilizable sugars. The monosaccharides, glucose, fructose, and galactose, on the other hand, are readily and completely utilized, although by different rates and means of absorption, diffusion, utilization, and excretion.[1] Also in contrast to other sugars, sucrose is not detectable by the ordinary reducing solutions and consequently would likely go unnoticed on a routine urinalysis. However, by submitting the urine to a few drops of concentrated acid and heating for ten minutes, hydrolysis will take place, and a Benedict's test will be positive.

Because of its very poor reabsorption by the kidney, intravenous solutions of sucrose have been used as a measure of extravascular space and of glomerular filtration rate, closely paralleling that of inulin. It has also been suggested in the past as an effective agent to reduce spinal fluid pressure when given as a hypertonic solution, as it does not enter the subarachnoid space or the cells and escapes only through the urine. Damage to renal tissue has been reported from the use of these solutions, but it appears to be only temporary, and damage to other tissues has not been reported.[2]

Landensuu[3] has shown that ingestion of large amounts of sucrose, such as often will happen in bottle-fed babies, may effect a spillover into the urine of normal children, but even this appears to have rather definite limitations. Dr. L. I. Woolf[4, 5] of this hospital found 25 mg. per 100 ml. to be the upper limit of normal in postprandial specimens in normal infants. However, considerably more investigation is needed to establish the normal ranges in different situations.

Some children with gastroenteritis who are otherwise normal have been reported to show an excess of sucrose in the urine. Reuss,[6] in 1910, recorded twelve instances of "saccharosuria" in children severely ill with gastroenteritis, and more recently Owen and Lewis[7] reported six patients with sucrosuria, three of whom died and five of whom had gastroenteritis. The

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sixth infant died on the seventh day of life of an undiagnosed condition associated with jaundice and hepatosplenomegaly. One of the three survivors had an abrupt disappearance of sucrose from the urine when switched to Dextri-Maltose, and in one the appearance of sucrosuria was first noticed after the gastroenteritis had subsided. In neither of these reports, however, is it mentioned whether the abnormal amounts of sucrose disappeared from the urine on follow-up examination.

In 1954, Moncrieff and Wilkinson[8] of this hospital recorded three infants who showed sucrosuria on normal diets when their urine was examined by paper chromatography. All three were mentally defective and had hiatal hernia. It was found that an ordinary milk feed (i.e., containing sucrose and lactose) caused an abnormally large excretion of sucrose, lactose, fructose, and, occasionally, glucose. On a sucrose-free diet the sugar excretion was normal. Sucrose, without lactose, caused only a slight increase in excretion of sucrose. Various combinations of sugars were given and there appeared to be some sort of interaction between sucrose and lactose. When these sugars were given together, other sugars also appeared more easily in the urine, although there was a considerable amount of individual variability among the patients studied. Since glucose and fructose appeared in the urine after the administration of sucrose, and one post-mortem sample of intestinal juice actively split sucrose and lactose, it was postulated that the error is more likely one of abnormal absorption rather than failure of digestion of these sugars. The link between the three component parts of this syndrome appears highly suggestive, but by no means conclusive. A number of children with hiatus hernia have been found to have no abnormality of sugar metabolism. Likewise, a number of congenital anomalies of the brain, including marked hypoplasia of the corpus callosum, were found in one child with the syndrome who died. A subsequent encephalographic examination of one of the surviving patients has shown only cortical atrophy.

Since the appearance of the three reported cases, a number of other children who have suggestions of a similar syndrome have been investigated. Four of these distinctly show mental deficiency, hiatal hernia, and varying degrees of sucrosuria. These cases will be reported in some detail. The remaining cases are somewhat less definite and are included merely to note the frequent association of sucrosuria with at least one of the other two findings (Table I). It should be reiterated that in searching for these patients a number (approximately 18) were found who had hiatal hernia and no sucrosuria demonstrated at the time of investigation. Of these, at least 6 had some degree of mental deficiency. The urine sugars were identified by one dimensional paper chromatography by Dr. L. I. Woolf[5, 9] of this hospital, and their approximate concentrations were measured.

CASE REPORTS

CASE 1.—L. P., a 7-month-old girl, was admitted to The Hospital for Sick Children, Great Ormond Street, on June 7, 1955. She was the only child of an Rh-negative mother who had had one previous miscarriage. The birth was normal and no jaundice was noted. Birth weight was 6 pounds 4 ounces. She had a partially cleft palate. She was spoon-fed with expressed breast milk for the first two months and then fed by bottle. She had tended to vomit since birth, and this became progressively worse from the age of 3 months on, when solids were added. Vomiting usually occurred immediately after feeding and was often associated with coffee ground

TABLE I. SUMMARY OF THE REMAINING EIGHT CASES DEMONSTRATING SUCROSURIA (Sugars Expressed in Milligrams Per Cent)

CASE	AGE	SEX	URINARY EXCRETION OF SUGARS WITHIN 4 HOURS AFTER INGESTION OF 1 OUNCE OF SUCROSE IN MILK	GASTRO-INTESTINAL SYMPTOMS	MENTAL DEFICIENCY	REMARKS
5. P. C. 243851	18 mo.	M	S — 100 F — 50 L — 25 (not repeated)	Vomiting No H.H.	Marked	No hiatus hernia on x-ray but improved on propping up. Twin brother normal
6. M. N. 240812	3 yr.	F	S — 60 F — 80 L — 12 (not repeated)	H.H.	Marked	Also had phenylketonuria; died
7. C. B. 262026	6 wk.	M	S — 50 L — 200 Twice repeated with similar results	H.H.	Probable	(1) Traumatic delivery with probable cerebral damage (2) General spasticity (3) Idiopathic scoliosis
8. D. G. 236092	2 yr.	M	S — 120 F — 50 Gl — 1000 Repeat normal (3 mo. later)	H.H.	Moderate	(1) Normal blood sugar (2) Microcephalic
9. G. B. 240466	8 yr.	M	S — 140 Others normal Repeat normal (3 mo. later)	H.H.	Mild	Sucrose-free diet for 8 months made no difference
10. D. M. 203622	2 yr.	M	S — 250 F — 60 Gal — 12 Repeat normal	None	Mild	Admitted for marasmus. Sucrose disappeared from urine coincident with improvement of general condition and mentality
11. D. W. 255350	9 mo.	M	S — 120 L — 90 Not repeated	H.H.	None	Doing well generally
12. P. W. 266918	7 mo.	F	S — 70 L — 120 Repeated after 1 wk. on sucrose-free diet S = 40, L = 120	H.H.	Questionable	Remarkable improvement coincident with sucrose-free diet. Continued improvement after being put back on sucrose

S = sucrose, L = lactose, F = fructose, Gl = glucose, Gal = galactose, and H.H. = hiatus hernia. All accompanying illnesses are noted in the remarks column.

material. She was retarded in her development; at the age of 7 months she did not lift her head, recognize her mother, or show any interest in her surroundings. The family history was noncontributory except that the father had tuberculosis and was in a sanatorium at the time of the infant's birth.

Physical examination revealed a backward, fretful, slightly microcephalic baby whose head circumference measured 15 inches. She weighed 12 pounds 10 ounces, and she had bilateral inguinal hernia. Other than the retardation, examination of the central nervous system failed to reveal abnormalities.

An x-ray examination of the esophagus revealed a moderate-sized hiatal hernia with free reflux and persistent irritability of the lower end of the esophagus. The hemoglobin was 8.3 Gm. per 100 ml. On a sucrose tolerance test she excreted 700 mg. per cent sucrose and 120 mg. per cent lactose four hours after being fed one ounce of sucrose in six ounces of milk. She was discharged to the outpatient department on Aludrox. Propping up was prescribed.

The vomiting persisted with occasional streaking of blood; however, repeat x-ray examination did not demonstrate a stricture of the esophagus, and surgery was not considered advisable. She was readmitted in July, 1956, when a lumbar encephalogram was done in view of the previously reported case of sucrosuria with hypoplasia of the corpus callosum. This revealed bilateral cortical atrophy with no evidence of agenesis of the corpus callosum. The vomiting had ceased, but the child was grossly and severely retarded. She has since been institutionalized.

Case 2.—R. T., a 13-month-old boy, was admitted on Jan. 12, 1956, having had a hiatal hernia diagnosed elsewhere by barium swallow at the age of 3 months. He had been born by a breech delivery, weighing 5 pounds 5 ounces, and presented some difficulty in resuscitation. He refused feeding early, and tube feeding was necessary. He is the only child of healthy parents, and there was no history of mental retardation in the family. Development was moderately delayed. His symptoms of vomiting and hematemesis had been considerably improved by thickened food and by being propped up.

Physical examination revealed a retarded child with a flat forehead and wide-set eyes. The skull circumference was 17 inches. Weight was 14 pounds. There was no evidence of mongolism or cretinism, although the serum cholesterol was slightly elevated. This was normal when tested later. A barium swallow confirmed a large intrathoracic gastric pouch, and esophagoscopy on Jan. 20, 1956, by Mr. David Waterston, showed no stricture and very mild esophagitis. The hemoglobin was 12.6 Gm. per 100 ml. The urine was negative for phenylpyruvic acid, but on paper chromatography it showed 100 mg. per cent sucrose and 40 mg. per cent lactose four hours after the ingestion of one ounce of sucrose in six ounces of milk. Urinary 17-ketosteroids were 1.38 mg. per liter. Bone age was delayed.

An intelligence quotient on Feb. 2, 1956, using the Griffiths Developmental Scale, was performed by Mr. Stephen Coates and recorded as 67.

The patient was discharged to the outpatient department on a sucrose-free diet but continued to vomit, with occasional hematemesis. On May 7, 1956, repeat esophagoscopy by Mr. Waterston revealed more severe esophagitis, and a repair of the hiatus hernia was undertaken. The postoperative course was satisfactory, and the child has vomited considerably less since that time.

He was readmitted in October, 1956, for a lumbar encephalogram, which showed widening of the parietal sulci but no abnormalities of the corpus callosum. At this time he was 22 months old and had been on a sucrose-free diet for 8 months. He was still retarded but could walk with support, and his mother could recognize monosyllabic speech. A repeat sucrose tolerance test was normal and he was returned to a sucrose-containing diet. After one week he still showed no abnormal excretion of sucrose. He was discharged on a normal diet to the outpatient department.

CASE 3.—T. P., a 7-month-old girl, had been born normally weighing 5 pounds 13 ounces. She took feedings poorly at first, and at the age of 3 months had a frenotomy for tonguetie. She gained weight normally and had little vomiting until the age of 6 months, when she began to vomit fluids especially. She was seen in the outpatient Department at The Hospital for Sick Children, and a barium swallow at that time revealed a supradiaphragmatic portion of the stomach which was regarded as a hiatal hernia of the sliding variety. She was placed on thickened feedings and was propped up and improved considerably. She remained well until Jan. 12, 1956, when she was admitted at the age of 11 months with pneumonia, recurrent vomiting, and general failure to thrive for the previous 4 weeks. She had sat alone at the age of 8 months, but she had not progressed since then and was considered backward in comparison with her siblings.

Physical examination revealed a limp, pale child who appeared chronically ill and backward. Chest x-ray revealed collapse in the right upper lobe and the basal segments of the left lower lobe. This improved markedly on Aureomycin. Mantoux skin test 1:100 was negative, as were gastric washings for acid-fast bacilli. A repeat barium swallow failed to reveal a hiatal hernia. The hemoglobin was 5 Gm. per 100 ml., the erythrocyte sedimentation rate was 29 minutes in one hour. The white blood count was 12,500 with 48 per cent polymorphonuclear and 52 per cent lymphocytes. Blood chemistry, blood urea, serum calcium, plasma proteins, and electrophoresis tests were all normal. A sucrose tolerance test showed an excretion of 125 mg. per cent sucrose, 20 mg. per cent fructose, and 25 mg. per cent lactose two hours after ingestion of one ounce of sucrose. The urine was free of phenylpyruvic acid. Observation on the ward confirmed retardation of a moderate degree. The chest symptoms were considered to be due to inhalation of regurgitated material from the hiatal hernia. The vomiting resolved on thickened feedings and propping up, and she was discharged to the outpatient department on Feb. 8, 1956. Periodic visits since that time have shown improvement in motor skills. She is now starting to walk at 26 months and has very little vomiting. The urine has not been tested recently for sucrose.

CASE 4.—N. F., an 8-month-old boy, was admitted to The Hospital for Sick Children on July 29, 1955, for complaints of regurgitation with occasional hematemesis since birth. He was born weighing 7 pounds 8 ounces following a normal pregnancy and delivery. Four hours after birth he had a severe cyanotic attack and for the first week was lethargic. He was breast-fed with considerable difficulty. Regurgitation became marked and necessitated tube feeding for the next 2 months at another hospital. He then took food but continued to vomit and had several episodes of vomiting frank blood and mucus. During one of these episodes he had pneumonia from aspirated vomitus, necessitating further hospitalization.

His development was delayed, and he did not notice objects until 6 months or hold up his head until 7 months of age.

Physical examination revealed a retarded baby with mild hypertelorism and a flat face. Head circumference was 16¼ inches. He was unable to sit. The grasp reflex was still present, and the weight was 15 pounds.

Barium swallow demonstrated an abnormal grossly dilated esophagus, but no definite herniation. Esophagoscopy by Mr. Waterston showed a wide upper esophagus but no esophagitis. The cardia appeared normal and without reflux. A small erosion in the mucus of the cardia was noted. The hemoglobin was 10.36 Gm. per cent. The urine contained no phenylpyruvic acid, and on paper chromatography at this time it was negative for sucrose or other sugars. He was discharged in two weeks, having improved slightly on propping up after meals and Aludrox.

He continued to vomit blood and failed to gain weight over the next four months and was readmitted on Nov. 29, 1955. His hemoglobin was 7.5 Gm. per cent and he was transfused with 500 c.c. of packed cells to 11.6 Gm. per cent. Repeated esophagoscopy revealed mild esophagitis above the cardia.

Urine chromatography was repeated, and following an ounce of sucrose in six ounces of milk the urine contained 350 mg. per cent sucrose and 150 per cent lactose. A week later after ingestion of one-half ounce of sucrose he excreted 70 mg. per cent sucrose and 50 mg. per cent lactose.

He was placed on a sucrose-free diet and transferred to the hospital's country branch at Tadworth. Meanwhile, he had developed marked eczema and asthma, and it was noted that he was deaf.

After 5 months at Tadworth, on May 25, 1956, he was discharged home slightly improved mentally. He died at home on June 4, 1956 of pneumonia following aspirated vomitus. A postmortem examination was not done. No further urinary determination for sugars had been made.

DISCUSSION

It might be noted that lactose frequently appears in rather large quantities, sometimes considerably greater than sucrose, so that the metabolic defect would in fact appear to be a "disacchariduria." However, its appearance is too inconsistent to draw any conclusions, and this is another aspect that must remain in the realm of future investigation.

If there exists a cause-and-effect relationship of the different lesions, i.e., the metabolic defect, the mental deficiency and the anomaly of the lower end of the esophagus, it remains obscure. In one patient (Case 4) previously normal chromatography of the urine later revealed an excessive secretion of sucrose. This child failed to show any improvement other than what might be expected from constant medical care, and he died shortly after being discharged from the hospital. On the other hand, four of the patients on whom repeated studies had been done (Cases 2, 8, 9, and 10) reverted to normal. In at least two of these (Cases 2 and 10) and possibly in a third (Case 9) this reversion coincided with a general improvement in mentality and general physical well-being. Here again the evidence is far from conclusive, but it might be postulated that the metabolic defect—be it a failure of enzymatic digestion or of faulty absorption from the intestinal mucosa—might at least be transitory in a number of cases, and resumption of normal metabolism in these cases may reflect, or possibly initiate, a general improvement in the other manifestations. The temptation to link the three conditions more specifically is thwarted by several factors. In these cases there are a number of causes for mental deficiency that are separate within themselves, e.g., phenylketonuria, birth trauma, and microcephaly. Also, as previously mentioned, there were several patients with mental deficiency and hiatal hernia who did not show sucrosuria. Possibly some of these might represent a transient defect which was missed on the one examination. Nevertheless, it seems more than mere coincidence that this number of cases should present with a similar kind of findings, and it is hoped that further investigations will elucidate matters.

Case 12 is interesting in that a sucrose-free diet was tried for one week only and was coincident with a notable improvement in weight gain and general well-being for the first time since birth. This continued until discharge, in spite of the reintroduction of sucrose in the diet. In the two patients that were put on a sucrose-free diet over a period of time (Cases 4 and 9) no discernible difference was noted, but this seems a reasonable program to be tried more persistently in the future. Certainly in galactosemia there seems to be a relationship between the presence of an abnormal sugar and mental retardation, and improvement usually occurs when lactose is removed from the diet.

No new factual observations can be made as to the mechanism of the metabolic defect in this report. It may be postulated, perhaps, that the inconsistency of the finding of sucrosuria in the previously mentioned four cases would tend to incriminate periodic abnormal absorption of the disaccharides from the intestines rather than a faulty enzyme system. On the other hand, the possibility cannot be ruled out that a certain amount of maturation of an immature enzyme system may occur to the extent that hydrolysis of the disaccharides may ensue properly. This would more likely be a variation of the quantity rather than the efficiency of the enzyme present.

SUMMARY

Twelve cases are reported wherein sucrose was found in the urine in association with mental deficiency and an anomaly of the lower end of the esophagus.

In this brief report no conclusions regarding the cause and effect relationship can be drawn.

The helpful assistance of Professor A. A. Moncrieff, Dr. R. H. Wilkinson, and Dr. L. I. Woolf is greatly appreciated. Thanks are also due to the consultant staff of The Hospital for Sick Children, Great Ormond Street, for their kind permission to use the cases.

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MEGIMIDE IN THE TREATMENT OF SEVERE BARBITURATE POISONING

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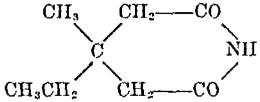
THERE have been numerous controversial reports in the literature[1, 2] on the treatment of barbiturate poisoning in children. In the past six months at St. John's Hospital, we have had a new experimental drug for use in barbiturate poisoning called Megimide.

Megimide,* brand of B-ethyl-B-methylglutarimide, is a colorless crystalline compound with the structural formula:



Its solubility in water at neutral pH and at room temperature is only 0.5 per cent. This is an advantage in that its low solubility minimizes the risk of overdosage. So far, no severe contraindications, have been demonstrated.

The pharmacology of Megimide has been investigated by Shaw and Harris,[3, 4] using rats, mice, rabbits, and dogs. Megimide is effective orally as well as intravenously or intraperitoneally. Plum and Swanson[5] stated: "B,B-Methylethylglutarimide showed little evidence of true barbiturate antagonism but appeared to possess nonspecific analeptic properties. The analeptic effects were more rapid in onset than those of picrotoxin, and there were fewer undesirable side reactions." Boyan and co-workers[6] feel that "the most satisfactory results have been obtained in patients who have taken less than 2 gm. of barbiturate and have been in coma less than twelve hours."

Harris[7] demonstrated its action and effects upon patients under clinical anesthesia. Both Shaw and Harris[4, 7] have demonstrated a wide margin of safety; the symptoms of overdosage are excitement and restlessness on awakening, exaggerated reflexes, vomiting and wretching, and slight muscular twitchings of the fingers, arms, and isolated facial muscles. This is easily controlled by sedation with paraldehyde or a short-acting barbiturate.

Megimide is supplied as a 0.5 per cent solution in vials containing 100 c.c. or in vials of 50 mg. per 10 c.c. normal saline. It is given intravenously slowly, the amount depending on the weight of the patient, and is repeated every five to fifteen minutes depending on the response of the patient, the aim being to bring the patient to a light plane of anesthesia where he can be easily aroused. There is no recommended dosage schedule according to weight; the amount given is determined by the response of the patient. Shaw and associates,[4] working with dogs, showed that Megimide

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*Megimide was obtained from Muller & Phipps, One Park Ave., New York 16, N. Y.

in doses of 15 mg. per kilogram of body weight caused convulsions, and that when the dose was 30 mg. per kilogram of body weight, the convulsions were fatal. Treatment before or after the injection of Megimide prevented the convulsions. They injected up to 60 mg. per kilogram of body weight of Megimide following treatment of the dogs with pentobarbital, and no convulsions occurred.

During the intravenous administration of the drug, the individual should be assessed after each injection by a recording of the pulse rate, respiratory rate, blood pressure, muscle tone, deep tendon reflexes, eye movements, pupillary light reaction, temperature, and skin color.

Once the patient has reacted, it is seldom necessary to administer additional therapy. Further therapy is necessary when coma has been prolonged before treatment or a long-acting type of barbiturate has been the etiologic agent.

It should be emphasized that no one agent is the complete answer in the treatment of barbiturate poisoning since therapy is threefold—the treatment of coma, of circulation, and of respiration. The use of analeptics and similar drugs is still controversial in the treatment of coma, but Megimide seems to be a definite addition to our present armamentarium. Circulation has to be maintained, at times by infusions with vasopressor agents, the rate of the infusion being guided by blood pressure observations. Respiratory depression has to be counteracted, if necessary by artificial methods. Tank respirators or anesthesia apparatuses such as positive pressure breathing devices, or the like, and oxygen may be used. An upper respiratory airway must be maintained, by suction, airways, or, when needed, by tracheotomy. Positioning of the patient is important for pulmonary and oral drainage and as an aid in the combating of shock. Adequate hydration should be maintained by intravenous infusions, and excretion of urine should be checked, the patient being catheterized if necessary. Antibiotics should be used liberally for the prevention of secondary bacterial complications.

CASE REPORT

A 13-month-old male infant ingested approximately 10 grains of amobarbital (Amytal) at noon, July 27, 1957. Approximately one hour later the infant fell asleep, and at 4:30 P.M., his mother was unable to rouse him. He was taken to the emergency room of St. John's Hospital and admitted to the pediatrics department at 5:00 P.M., and therapy was started.

Physical Examination.—The infant was pale and cyanotic, and the extremities and body were cold and clammy. It was impossible to arouse him even by painful stimuli. Blood pressure was unobtainable. Respirations were irregular and shallow, 3 to 5 per minute. Pulse was 160 per minute. Temperature was 97° F. rectally.

The head was symmetrical. Other findings were: eyes, pupils pinpoint round, did not react to light; ears, no abnormality; nose, mucus secretion draining from nares; mouth, filled with secretions, no gag reflex noted; neck, supple.

The chest was symmetrical. The lungs were clear to percussion and auscultation. The heart sounds were of good quality; no murmur was heard; the rate was rapid (160) and regular.

The abdomen was soft. There were no masses and no organ enlargement. There were no deformities of the extremities.

Deep tendon reflexes were hypoactive.

Laboratory Examination.—A 24 c.c. urine sample obtained by catheter on admission showed 0.6 Gm. per cent, calculated as phenobarbital.

Course.—The patient was immediately given oxygen by mask and artificial respiration was induced. Suction was used and a stomach tube was passed, but very little fluid could be obtained by suction and the tube was removed because of the child's poor condition. A pharyngeal airway was introduced and antibiotics were given intramuscularly. An intravenous infusion of 500 c.c. of 5 per cent glucose in water containing 2 c.c. of Levophed* was started promptly. Picrotoxin was given through the intravenous tubing for the next forty-five minutes, 0.5 c.c. every fifteen minutes, but the child responded only slightly and his condition deteriorated.

Megimide solution was then given through the intravenous tubing, 3 to 5 c.c. every five to fifteen minutes for the next one and one-half hours, until the child was brought to a plane of light anesthesia. At this time he could be easily aroused; his pupils, which were pinpoint, were normal; and he cried when aroused by light stimuli. Within the next hour he took fluids fairly well, and no further artificial respiration or intravenous fluids were needed. Oxygen was administered occasionally for the next three hours. The child received a total of 150 mg. of Megimide.

No regression occurred, and by the next morning, twelve hours after Megimide was given, the child, although groggy, responded well to verbal and tactile stimuli. Twenty-four hours later, he was alert and active, and he was discharged from the hospital on the third day.

SUMMARY

1. A case of severe barbiturate poisoning is presented.

2. The treatment with Megimide and supportive therapy is reviewed.

We wish to thank Dr. Lundy and the Mayo Clinic for the first supply of Megimide for the Anesthesia Department of St. John's Hospital. We also thank Sister M. Rudolpha, O.S.F., Sister M. Seraphia, O.S.F., and Sister M. Floretta, O.S.F., under whose supervision Megimide was given.

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*Levophed was obtained from Winthrop-Stearns, Inc.

MALATHION POISONING IN A 34-MONTH-OLD CHILD FOLLOWING ACCIDENTAL INGESTION

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MALATHION is a relatively new, widely used insecticide of reputedly low toxicity. To our knowledge, there has been no published case of human poisoning with this product. Consequently, it is felt worthwhile to present our experience with an instance of malathion poisoning resulting from its accidental ingestion by a child.

Malathion is a member of the organic phosphorus insecticides among which are also found parathion and T.E.P.P. (tetraethyl-pyrophosphate). Chemically these compounds are esters of phosphoric acid or of its derivatives. This class of compounds was first investigated in Germany during World War II in search of a new "War Gas." Records of this search were captured at the war's end by the English and the Russians. In 1947, a portion of this material deemed of no military significance was published by the English and led to the development of the organic phosphorus insecticides. The first of these products, parathion and T.E.P.P., are extremely toxic compounds. However, because of their effectiveness they are widely used in agricultural operations. Even though specially trained personnel are generally used for this work, an impressive number of fatal poisonings have occurred. Most of these deaths resulted from absorption of the insecticides through the unbroken skin. Inhalation, especially with aerosol preparation, has been another factor in these accidents. Fatal accidental ingestion in children has been reported. Effective insecticides which are less toxic to man are being sought by industry. Malathion, which by animal experiments appears to be one hundred times less toxic than parathion, has been one of the resulting products.

The mechanism of action of all the organic phosphorus insecticides, including malathion, is the inactivation of cholinesterase, an enzyme responsible for the hydrolysis of acetylcholine.[8] Because of the importance of the acetylcholine cholinesterase system throughout the animal kingdom, these compounds are toxic to man and other animals as well as to insects. Since the same pharmacological effect, inactivation of cholinesterase, is responsible both for its insecticidal efficacy and for its toxicity, it would seem likely that any compound useful as an insecticide would be toxic to man.

CASE REPORT

D. B., a 34-month-old male, was in good health prior to the day of admission. At 5:30 P.M. on that day, he was outdoors with a playmate. The playmate took a bottle of insect spray from the glove compartment of his father's truck and gave it to the patient, who proceeded to drink from it. This was observed from a window by

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From the Division of Pediatrics, North Shore Hospital.

the patient's mother. Immediately after ingestion the boy coughed, then appeared to be perfectly normal. He was immediately given a glass of milk, a hard-boiled egg, and milk of magnesia.

Fifteen minutes after ingestion, the child suddenly became limp and slumped over the table. He was taken to the office of a physician, who noted muscle flaccidity, miosis, and drooling. His stomach was lavaged and the contents were noted to have an odor corresponding to that of the insecticide.

The patient arrived at the North Shore Hospital one hour and forty minutes following ingestion of the spray. He was noted to be stuporous, retching, and to respond only to painful stimuli. His respiration was rapid and noisy, the face was flushed, and the child appeared to be severely and acutely ill. The temperature was 100° F., pulse 120 per minute, respiration 35 per minute, blood pressure 95/50, weight 21 kilograms. The pupils were pin point, equal, and did not respond to light. A large quantity of saliva and mucus was present in the oropharynx. There were no lesions of the buccal mucosa or pharynx. The neck was not stiff and the trachea was in the midline. The apical rate was 120 per minute with a soft systolic murmur along the left sternal border. The second pulmonic sound was louder than the second aortic sound. The heart was not enlarged. The lungs were dull to percussion at both bases. Both lung fields were full of fine, medium, and coarse moist râles most marked at the bases, and scattered expiratory wheezes were noted. The abdomen was soft, and hyperactive bowel sounds were heard. The deep tendon reflexes were absent and the Babinski reflex was positive on the right side. Abdominal and cremasteric reflexes were present and equal. The gag reflex and response to painful stimuli were present. The child was incontinent of urine and feces although previously toilet trained. He vomited small quantities of food and fluid frequently.

The bottle labeled "Malathion Insect Spray, 50%" was examined, and 8 c.c. was found to be missing from the previously unused bottle. The contents were listed as 50% malathion, 38% xylene, and 12% inert ingredients.

The hemoglobin was 12.4 Gm., total white count 8,600, polymorphonuclear leukocytes 47 per cent, nonsegmented forms 5 per cent, lymphocytes 46 per cent, eosinophils 1 per cent, monocytes 1 per cent. The urine was yellow and clear, reaction 4.5, specific gravity 1.014, albumin 0, sugar 0, acetone 0, microscopic examination negative. A chest x-ray taken 5 hours after admission showed slightly increased markings bilaterally. Unfortunately, no determination of cholinesterase levels was made.

Gastric lavage was performed to prevent aspiration. A large quantity of brownish fluid containing partially digested food was removed. The gastric contents had an odor corresponding to that of the insecticide. The child was placed in an oxygen tent and frequent suctioning of the profuse oropharyngeal secretions was necessary. His respiratory distress increased and slight cyanosis was noted. One hour after admission, atropine, 0.3 mg., was given half intravenously and half subcutaneously due to the thrashing about of the patient. However, just before the drug was given, the child began to improve rapidly. His respiration became less labored and he became more responsive. Two and one-half hours following admission (three hours and forty minutes after ingestion of the insecticide) the child was conscious, alert, oriented, and in no respiratory distress. His lungs were completely clear to percussion and auscultation. The pupils were in mid-miosis and reacted to light. Ptyalism was no longer present.

Three hours after admission, the patient again began to have respiratory distress. This time it was characterized by a barking cough, inspiratory stridor, retractions, and an increased respiratory rate. No râles were heard and it was felt that these symptoms did not result entirely from the anticholinesterase effect of the insecticide, but also from the local irritating qualities of the malathion and xylene. High humidity by means of a nebulizer was added to the oxygen tent. Five hours after admission the patient was asymptomatic and no signs of intoxication were observable clinically.

DISCUSSION

The symptoms of malathion and other organic phosphorus poisonings are entirely, as far as has been determined, secondary to the inactivation of cholinesterase.[8] The normal hydrolysis of acetylcholine does not occur, resulting in the accumulation of this product at all the sites at which it is normally found. These include pre- and postganglionic parasympathetic fibers, preganglionic sympathetic fibers, myoneural junctions, and in all probability the central nervous system. The parasympathetic postganglionic (muscarine-like) effects include: miosis; excessive secretion of the salivary, sweat, bronchial, and lacrimal glands; bronchoconstriction, pulmonary edema, and cyanosis; hypermotility of the digestive and urinary tracts resulting in vomiting, defecation, and urination. The preganglionic sympathetic effects may account for the "reversed effects" such as mydriasis occasionally noted early in these intoxications. The effects on the central nervous system and on the myoneural junctions may result in headache, restlessness, anxiety, tremors, convulsions, muscular twitches, drowsiness, and coma. Therefore, a typical organic phosphorus poisoning may develop symptoms of headache, weakness, and fatigue within one to two hours after exposure. These symptoms are rapidly followed by dizziness, nausea, abdominal cramps, vomiting, and diarrhea. Miosis and difficulty in focusing are noted. Dyspnea, a feeling of constriction of the chest, profuse sweating, hypersalivation, mental confusion, and twitching of the muscles followed by convulsions, coma, pulmonary edema, and death may occur in severe poisoning. Although the signs of parasympathetic stimulation including miosis are the most characteristic and constant signs of poisoning, it must be emphasized that the presence or absence of any single sign is not pathognomonic of organic insecticide poisoning. Miosis, for example, may be absent early in the poisoning and mydriasis has been reported.[1] This may be explained by the simultaneous stimulation of preganglionic sympathetic fibers. Even in these cases, however, miosis was present later in the course of the illness. Delay in the institution of specific therapy because of the absence of miosis or of any other single sign is not justified.

The only significant laboratory determination in cases of organic phosphorus insecticide poisoning is that of inhibition of cholinesterase activity in both plasma and erythrocytes. This finding of depressed cholinesterase activity is a constant finding in cases of poisoning and precedes even the onset of symptoms.[8] Symptoms of poisoning usually occur when the plasma and red cell cholinesterase levels are below 50 per cent. Normals for red cell cholinesterase are 80 to 120 per cent, while that for plasma cholinesterase is from 60 to 250 per cent. A presumptive diagnosis of organic phosphorus poisoning may be made when the red cell and plasma cholinesterase levels fall below 75 per cent. There is no other known condition in which red cell cholinesterase is lowered. Plasma cell cholinesterase, on the other hand, may be lowered by a variety of chemicals and by disease states, particularly of the liver. It is interesting to note that while symptoms of poisoning are usually no longer evident after twenty-four hours, the red cell cholinesterase remains depressed for from one to two weeks. Cumulative poisoning is therefore possible.

Cholinesterase activity may be determined by a number of methods,[4] most of which are based on the determination of the quantity of acetic acid liberated from a test system by a known quantity of blood. If laboratory facilitates for the performance of this determination are not available, samples may be sent to the U.S. Public Health Service for analysis.[3]

''Instructions for drawing, preparing, and shipping blood samples for cholinesterase determinations.'' (Clinical Memoranda, TDL 1 April '55)

''Blood should be taken by venipuncture from the arm of the subject by the ordinary procedure, using sterile equipment. Heparin is the anticoagulant of choice, and the minimum amount to prevent clotting should be used, so as to dilute the blood sample as little as possible. Merely wetting the syringe with heparin is sufficient. Sodium citrate may be used if heparin is unavailable. The blood should be carefully transferred from the syringe to a clean, dry 15-ml. graduated centrifuge tube by gentle pressure on the plunger. The needle should be removed, and the aperture of the syringe should be placed in contact with the side of the tube before the blood is forced out. These precautions are necessary to prevent hemolysis. Ten milliliters of blood should be drawn and processed to insure adequate amounts of material for cholinesterase analyses in duplicate to be done.

''The collected blood is centrifuged for 15 minutes at 2,000 rpm, and the plasma is separated. The plasma may now be placed in a clean, dry test tube of suitable size, closed with a tight-fitting *rubber* stopper, and plainly labeled. The plasma is now ready for shipment.

''The cells are mixed with three times their volume of isotonic saline (0.9 per cent sodium chloride) solution in the same centrifuge tube and again centrifuged at 2,000 rpm for 15 minutes. After discarding the supernatant fluid the operation is repeated, centrifuging this time for 20 minutes at 2,000 rpm. (In this final centrifugation the packing of the red cells is a critical point, and the recommended speed and time of centrifugation should be rigidly followed.) The volume of the cells is noted, and then the saline supernatant is removed to the point where the remaining volume of saline and cells is twice the volume of cells alone. The cells are then mixed thoroughly with the remaining saline. This mixture is then transferred to a clean, dry test tube, stoppered with a rubber stopper, and labeled. The red cells are now ready for shipment.

''Both plasma and cells must be kept refrigerated during shipment. It has been found convenient to individually wrap test tubes in cotton batting, and ship them, in contact with a 'refreezant' (a mass of silica gel packaged in plastic or metal and sold under a variety of trade names). 'Refreezants' are available from drug and sporting goods stores. They are intended for keeping picnic lunches and drinks cold. The device must be stored for 24 hours or more in a deepfreeze or ice-cube compartment of a refrigerator before it is ready for shipment. If one is on hand it is far more convenient than ordinary ice refrigeration. The refreezant will remain cold for 24 hours or more. It is recommended that shipments be made by air express, if feasible, in order to preserve adequate refrigeration for the samples during the entire period of shipment. Shipment may be made by slower forms of transportation, for short distances. In any event, mark all packages 'PERISHABLE,' 'RUSH.'

''Samples for analysis should be sent to the laboratory at P.O. Box 769, Savannah, Ga., or to the Field Station at Wenatchee, Washington, depending on which is nearer. The address of the field Station is P.O. Box 73, Wenatchee, Washington.''

TREATMENT

Malathion and other organic phosphorus insecticide poisoning may progress very rapidly to a fatal termination. Its treatment, therefore, presents a medical emergency. Since all the toxic effects of these products appear to be due to the accumulation of acetylcholine, atropine which blocks the action of acetylcholine on receptor organs is the drug of choice. The quantities of atropine required to treat this condition are in excess of the usual pharmacological dose. A medication schedule recommended by Grob and Harvey[6] for severe poisoning in adults suggests the immediate intravenous administration of 2 to 4 mg. of atropine followed by 2 mg. doses at 5- to 10-minute intervals until symptomatic improvement or signs of atropine toxicity occur. Intravenous atropine begins to show its effect in 1 to 4 minutes and reaches maximal effect in 8 minutes. Once atropinization is attained, it should be maintained for about forty-eight hours at a lesser dosage level which must be determined individually. Morphine and its derivatives are definitely contraindicated even in the presence of pulmonary edema because of their respiratory depressant characteristics.

After atropine has been given, the patient should be thoroughly washed with copious quantities of soap and water in those cases where skin absorption is suspected. The remainder of the therapy is supportive and symptomatic. The upper respiratory tract may require frequent aspiration for the removal of excess secretion. The maintenance of a clear airway and the administration of oxygen as well as provision for artificial respiration in the event of respiratory arrest may prove lifesaving. Convulsions may be controlled by the careful use of barbiturates.

SUMMARY

1. A case of accidental malathion poisoning occurring after the ingestion of about 8 c.c. of 50 per cent malathion by a 34-month-old child weighing 21 kilograms is presented. Symptoms began fifteen minutes after ingestion and consisted of coma, pulmonary edema, miosis, hypersalivation, muscle flaccidity, involuntary defecation and urination.

The diagnosis, pathologic physiology, symptomatology, and treatment of organic phosphorus insecticide poisoning is discussed.

3. It is felt that with the recent introduction of the organic phosphorus insecticides as products for the home and garden, physicians everywhere should be alerted to the possibility of such poisoning.

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THE RELATION OF PECTUS EXCAVATUM TO PECTUS CARINATUM

Classification of Anterior Chest Wall Deformities and the Effect on Treatment

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DEFORMITIES of the anterior chest wall primarily involving the sternum and costal cartilages, whether present at birth or developing with growth, are characterized by depression (pectus excavatum) or protrusion (pectus carinatum). At first glance these would seem to be entirely different, but when a sufficient number of both types of deformity are considered in all age groups it is found that their points in common are striking. The following observations and conclusions are based upon 171 cases treated surgically, an undetermined number of cases not operated upon for various reasons, and six autopsies on persons dying from causes not necessarily related to the deformity.

The depression deformities (pectus excavatum or funnel chest) are characterized by a backward curve of the sternum starting in the second segment and maximum at the xiphoid, and making the xiphovertebral distance abnormally short. The costal cartilages attaching to the sternum are likewise curved backward and a funnel-shaped depression is produced, with the lower end of the sternum the apex of the funnel. In infants and young children the lower end of the sternum is drawn back during inspiration, thus making a paradoxical motion. In older children this paradoxical motion is less and in adults the xiphoid may be stationary or even move forward during inspiration, but much less than the costal arch in the midclavicular line. There is a transverse groove like the Harrison's groove of rickets; the chest is flattened in the anteroposterior diameter; there is often a round back with occasionally a slight degree of scoliosis; and the heart is displaced to the left. In the younger children the deformity is usually symmetrical but in some of the older patients a definite asymmetry may be present with the right side of the chest more depressed than the left.

The protrusion deformities (pectus carinatum) present several types and usually do not appear until the child is 6 years of age or older. The protrusion may involve the sternum and then can take one of two forms. In one, the sternum protrudes in an arcuate manner with the greatest protrusion in the upper part of the sternum (pigeon breast); and in the other the sternum protrudes obliquely with the lower end of the sternum most prominent (pyramid chest). The arcuate type may resemble funnel chest but the distance between xiphoid and vertebral column is not decreased.

From the Hospital for Special Surgery.

In another type of protrusion deformity the sternum is but little affected and the protrusion is at the costochondral junctions. In most cases the protrusion is unilateral, but when protrusions are present on both sides they are at different levels unless in the costal arch, where they may be bilateral. If the protrusion is below the sternum the costal arch flares, and bilateral protrusion is more common at this level than higher.

A third type of anterior chest wall deformity seems to combine characteristics of the other two. There may be an arcuate type of protrusion but the lower end of the sternum may be drawn back so as to decrease the anteroposterior distance at the xiphoid. There may also be a true funnel chest with a lateral protrusion. In brief, the individual deformities differ among themselves and the one characteristic they have in common is that each presents features of both depression and protrusion.

The age at which the deformity appears is an important consideration. A great many of the depression deformities are present at birth or appear early in infancy; others are scarcely noticeable or absent in early childhood but appear later and develop rapidly especially during the period of increased growth associated with puberty. On the other hand, the protrusion deformities put in an appearance only after the child has had a chance to grow, although they do not necessarily wait for the more rapid growth of puberty.

The symptoms of funnel chest are respiratory and cardiac, or both, with the resultant effects on growth and development. The respiratory symptoms are those of chronic or unduly persistent pulmonary infection caused by ineffectual cough. The cardiac symptoms are due to pressure of the sternum on the heart and vary from slight exercise intolerance to inability to walk across the room.

The symptoms of protrusion deformities are also respiratory and cardiac but are usually less prominent than in the depression deformities. The respiratory symptoms are of the same type and cause, i.e., ineffectual cough. The cardiac symptoms, when present, also take the form of exercise intolerance but the cause is obscure.

The etiology and pathogenesis of the anterior chest wall deformities are discussed in a recent paper.[1] It is therefore only necessary to present them briefly here.

Heredity plays an important role in the etiology, but the hereditary trait is recessive and, hence, the forebear may not be found. Furthermore, heredity is specific only as to the site of the deformity and not as to the type. That is, the ancestor may have a depression deformity but the patient may have either a depression deformity or a protrusion deformity and it is not unusual to find both types of deformities in siblings.

The pathogenesis has two factors. One is the pull of the diaphragm and the other is the disproportionate growth of the ribs. The dominant factor determines the type of deformity.

In the depression deformities the pull of the diaphragm is responsible for the deformity and this pull is due to a short central tendon. The paradoxical motion of the xiphoid in an infant with a funnel chest during quiet respiration can be due to no other factor. In children who develop the deformity as they approach the age of puberty, it is assumed that a diaphragm, whose central tendon is only slightly shortened during infancy, has failed to grow at the same rate as the ribs.

The protrusion deformities can be explained on the basis of disproportionate rib growth in that some ribs grow proportionately longer than others. The ribs of normal length anchor the sternum or costal arch, hence the ribs which are too long must buckle at their weak point, which is the costochondral junction.

If the overgrown ribs are paired, the effect will be to push the sternum forward where they attach. Thus, overgrowth of the second and third ribs will cause an arcuate deformity, while overgrowth of the fifth, sixth, and seventh ribs will produce an oblique deformity, and overgrowth lower will make the costal arch flare.

If the ribs grow too long on one side only, the costochondral junction will still buckle but will protrude, thus making the deformity lateral to the sternum or, if lower, will produce a unilateral flare of the costal arch. If a funnel chest is present, unilateral overgrowth of the ribs will produce an asymmetrical depression deformity, although it is not apparent why the depression is always greater on the right.

In the depression deformity the short central tendon of the diaphragm restricts diaphragmatic motion and interferes with the cough mechanism. In the protrusion deformities the diaphragmatic action may also be impaired. This is because the diaphragm is too small for the large chest and the increased tension has lowered the dome, thereby decreasing its range of motion, or else the muscle is attenuated by stretching. In either case an ineffectual cough will result.

When both of the factors producing depression and protrusion deformities are present and the dominance of one over the other is not great, a combined deformity may result with certain characteristics of both. It is obvious that such deformities will not follow a set pattern, and although they can be grouped together each case must be considered individually.

A classification of the deformities of sternum and costal cartilages can then be made on the basis of pathogenesis.

Deformities of sternum and costal cartilages

I. Depression deformities (pectus excavatum, funnel chest)
    A. Congenital
    B. Developmental
        1. Symmetrical
        2. Asymmetrical
II. Protrusion deformities (pectus carinatum, pigeon breast)
    A. Midline
        1. Arcuate sternum
        2. Oblique sternum
    B. Lateral
        1. In upper five ribs
        2. In costal arch
III. Combination deformities

When treatment is necessary for these deformities, surgery must be employed; and the type of surgery cannot be the same for all groups. Because of the variations within the groups the time for operation and the extent of the operation may vary.

If the deformity is minor, no treatment is necessary. If the symptoms seem minor, however, it must be remembered that the patient has never been normal and he must be compared with normal children of the same age group as to activities, both physical and social. The depression deformities come to treatment more often than the protrusion deformities.

An infant with a well-developed funnel chest needs corrective operation, but because the procedure involves resection of five costal cartilages on each side and elevation of the sternum *it is better to postpone it until the age of 2 years or later.* However, if chronic or persistent cough, retarded development, restricted activity, or any other symptoms of consequence attributable to the deformity are present, it is safer to operate at a younger age than to wait. In the presence of a chronic pulmonary infection in an infant under the age of 1 year I prefer to use a simple sternoplasty which can be performed quickly through a small incision without the use of an endotracheal tube for anesthesia. The deformity may recur, but the baby has had a chance to recover from the pulmonary infection and develop in a normal manner for two years or more before the *radical operation is undertaken.*

Since the growth factor is important, a moderate depression without symptoms is better observed until the effect of growth can be ascertained, but operation should not be delayed if the chest is becoming flattened, round back or scoliosis is developing, or any other uncorrectable deformity appears. A relatively minor depression should be operated upon promptly if the heart does not shift to the left as the sternum encroaches upon it. A moderate deformity developing around the age of puberty should be treated surgically without undue delay. This is especially important if the deformity shows signs of becoming asymmetrical, because the greater the asymmetry the less satisfactory the correction. An asymmetrical deformity in a girl will cause the breast on the more depressed side to be smaller than the other. If operation is undertaken in an adult, a fairly satisfactory result can be obtained but less satisfactory than if the operation had been done at the proper time in childhood.

The psychological reaction in persons with chest deformities is important, and it is safe to say that any person who has enough deformity to cause embarrassment will obtain physiological as well as psychological improvement after adequate surgery. This applies to protrusion deformities as well as to depression deformities.

Since growth is the dominant factor in producing protrusion deformities, it follows that operation should not be undertaken in infancy and probably not until the approach of the age of puberty. There is a persistent and thoroughly mistaken idea that the correction of a protrusion deformity is only for cosmetic reasons. The symptoms produced by protrusion deformities, as mentioned above, are real and may be quite crippling. Surgical correction should be instituted as soon as the deformity becomes obvious, especially if it seems to be increasing. Also, when a breast overlies a protrusion deformity, its development will be affected, as in the depression deformities. The type of operation varies with the type of deformity, but the procedures which I have employed have been in the nature of a thoracoplasty, whether of ribs or sternum, and should be more extensive than would appear necessary to one unfamiliar with the condition.

SUMMARY

Depression and protrusion deformities of the sternum and costal cartilages belong in the same category because they have similar factors in etiology and pathogenesis.

The type of deformity is determined by the dominant factor.

The treatment is surgical.

The optimum age for the operation and the procedure employed must be determined by the type and extent of the deformity.

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AN OBJECTIVE SURVEY OF DENTAL MALOCCLUSIONS IN CHILDREN

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NATURAL and acquired deformities of the dental arches with malocclusions of the teeth are common in childhood. A disturbance of mastication, breathing and speech often results. In addition the condition is associated frequently with objective changes of the facial appearance that present a problem to the family and dentist at the time of social consciousness. A knowledge of these abnormalities at their onset may help in restricting their progress and further their correction. This has been found to be easier and more satisfactory during the early years of growth and development of the jaws.[1]

Usually the physician is the first to make professional examinations of the mouth and teeth of children when defects may be present or beginning. This places the physician in a position of responsibility for the early detection of abnormal deviations and the referral of significant lesions to dentistry for early evaluation or treatment in accordance with the advice of the orthodontist.

Although gross defects may be readily apparent, important variations of less degree may not be recognized easily. Precise analytical records of the dental structures can be made by casts, radiograms, and photometric procedures.[2] However, these processes are highly technical and are time-consuming and expensive. As such they are of service mainly in dentistry for obvious defects in the course of orthodontic treatment rather than being practical for pediatric screening tests for possible abnormalities. For this purpose no simple procedure is found in current use.

METHOD

To supply this a relatively easy graphic method has been developed for recording the position of the teeth and the shape of the dental arches. The plan was found to be useful for ready analysis of dental occlusions and for comparison with later graphs or a standard norm. The procedure was based on the direct recording of carbon prints of the contact surface of the teeth or their cusps by use of a so-called "Dentagraph Pack" (Fig. 1). The Pack consisted of a central pad or filler of 3 mm. thickness, made of 12 layers of soft paper toweling, between 2 plain white file cards. These were enveloped by a face-down strip of pencil carbon paper, and the assembly was stapled together near the open end.*

Imprints of the teeth on the file cards were made by insertion of one end of an individual Pack in proper position in the mouth with instructions to bite hard. This procedure recorded

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Address: 1838 Parkwood Ave.

*Dentagraph Packs were supplied on order by The Franklin Printing and Engraving Company, 228 Huron Street, Toledo 4, Ohio.

the prints of both arches directly by a single operation. Exceptionally, prints of unevenly erupted teeth were made by a separate Pack for each arch with the operator using a firm crosswise finger pressure against the dental crowns.

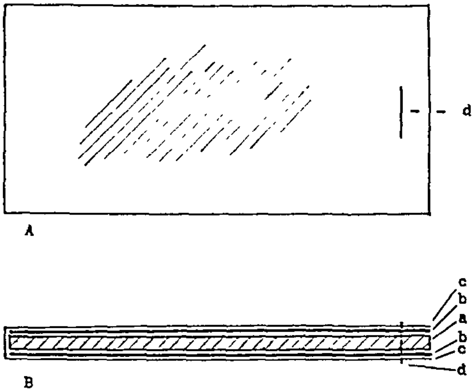

Fig. 1.—Dentagraph Pack. A. Plan view; sizes, 5 to 5.5 to 6 cm. wide by 10 cm. long. B. Side view: *a*, paper toweling filler; *b*, file cards; *c*, carbon paper; *d*, staple.

MATERIAL FOR STUDY

With well and willing children and a small incentive reward, this method was used in a consecutive series of 232 private office patients. These children were of the white race, aged 2 to 14 years, and had not had prior orthodontic care. The following results of the examination were classified in reference to the dental history, as obtained from the family.

A. Complaint-free or control.

B. Malformation, familial or individual; early dental loss.

C. Exceptional sucking habit.†

ANALYSIS

By comparison of each carbon print, or dentagraph, with the proper section of the Dental Print Guide (Fig. 2) and by the addition of a 1 mm. border outline around the cuspal clusters, the identity of the recorded teeth was made. With a pencil and millimeter scale ruler there was added the transverse base line *B* to connect the posterior cusps of the opposite temporary second molars or permanent bicuspids. Line *C* connected the opposite canines. And the vertical line *A* indicated the altitude of the canines in relation to the base line *B*.

The analysis of the results of this study was limited to the occlusal status of the lateral sides of the jaws. In normal occlusion it has been established that the posterior surfaces of the first and second temporary molars of both arches usually are in the same vertical plane, and the upper canines are located relatively posterior to the lower canines.[2] These designated relations, therefore, indicate a standard requirement for normal lateral occlusion.

Based on the position of the upper canines, the lateral occlusal status of each set of teeth was determined by the difference in millimeter lengths of the canine altitudes of the opposing arches. Thus, from the canine altitude of the upper jaw the canine altitude of the lower jaw was subtracted, and the *difference* was called the upper canine differential (UCD) value of the set of teeth. For normal occlusions this gave a negative (UCD –) value and, conversely, for abnormal ones, a postive (UCD +) designation.

CHARTING

The results of the survey were charted on a dotted scatter graph in panels showing the history, age, and range of UCD values (Fig. 3). In contrast to the control A group, this showed that the abnormal UCD + values were in greater ratio in the malformation B and the exceptional sucking habit C groups. The distribution of the abnormal occlusal range values within the history groups was summarized in Table I.

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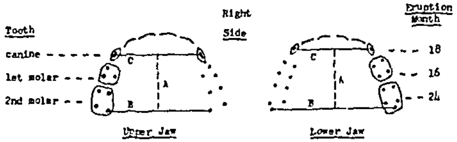
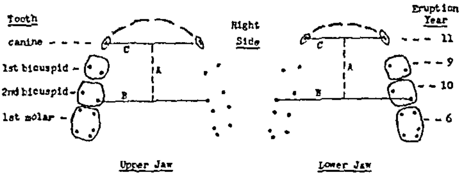
†Exceptional sucking habit is defined as a continuation of the sucking activity beyond the age of 3 years, after which time, further occlusal damage may not be corrected by the permanent dentition.[1]



I. TEMPORARY SET



II. PERMANENT SET

Fig. 2.—Dental Print Guide (diagrammatic), showing the carbon imprints of the contact surface or cusps with added dental border outline of the left side of each jaw. Construction lines: *B*, base; *C*, intercanine; *A*, canine altitude.

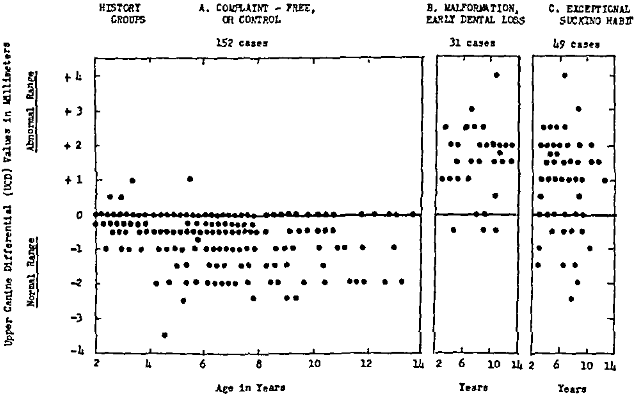


Fig. 3.—Age and history distribution of the upper canine differential (UCD) values for the normal (UCD −) and the abnormal (UCD +) groups in 232 children.

DISCUSSION

Although medical history is subject naturally to error and overlapping, and the number of tests in this series is small, there is noted a decided trend toward abnormal occlusal values in the malformation B and the exceptional sucking habit C groups (Table I).

TABLE I. DISTRIBUTION OF THE ABNORMAL OCCLUSAL RANGE VALUES OF THE OPPOSING DENTAL ARCHES OF 232 CHILDREN, 2 TO 14 YEARS OF AGE

HISTORY GROUP	TOTAL CASES	ABNORMAL OCCLUSAL RANGE (UCD +) CASES	
		NO.	PER CENT
A. Complaint-free, or control	152	4	3
B. Malformation, early dental loss	31	26	84
C. Exceptional sucking habit	49	32	65

The B group included 6 patients with a long-time absence of some temporary molars with abnormal occlusal values ranging to UCD + 2.5 mm. These prints commonly showed a loss of essential dental space, thus confirming graphically one of the major causes of malocclusion in childhood.[1] Nearly all patients in the C group within the abnormal occlusal range gave a history of the thumb-sucking type of habit. Within the normal occlusal range, together with the rest of the thumb-sucking types, there were included 9 of the 10 children who had variants of the sucking habit, such as finger, tongue, lip, nipple, and blanket. The inference, therefore, is that the latter forms of the exceptional sucking habit are usually harmless to lateral dental occlusion. And the duration and degree of the sucking habit would seem to be of importance mainly when the thumb is involved.

SUMMARY AND CONCLUSIONS

An intraoral, graphic method of recording, measuring, and evaluating the occlusal status of the teeth and dental arches in children has been described. The plan is proposed mainly for use as a pediatric screening test for select patients. The procedure is relatively quick, easy, and inexpensive.

A direct correlation was found between the dental history and the number of abnormal occlusal values to some extent in 65 per cent or more of cases in the hereditary malformation and exceptional sucking habit groups, in contrast to 3 per cent in the control group.

The practical application of this study would indicate, in addition to the routine oral examination for obvious defects of dentition, that a history be taken relative to familial abnormalities of the teeth and exceptional sucking habits. Direct referral of suspects of interested parents then should be made to dentistry for appraisal. Otherwise, screening tests of the dental arches should follow in those over 3 years of age with positive histories with a referral to dentistry of significant abnormalities.

When orthodontics is impractical in the exceptional sucking habit group, due to an early age of the patient or a persistence of the activity, other effectual ways of correction or restraint of the habit should be sought and recommended to a cooperative family.

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SPEECH PROBLEMS IN CHILDREN

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MANY pediatricians are faced with the common problem of whether to refer children for speech help, the age at which they should be referred, the perpetual question of whether they will outgrow their difficulty, and what type of speech problems can be helped. Many pediatricians are not even aware that such a person as a speech pathologist exists, and certainly very few understand the training or function of speech therapy. This article will discuss these and other questions relating to the field of speech.

That there are a total of four million speech-defective children in this country serves to emphasize the fact that speech is one of the most complex of human skills. During the utterance of a single word, almost a hundred muscles move. Muscles that manipulate the larynx must be timed exactly with those of the chest, diaphragm, and abdomen, and also with those of the face, mouth, and throat. All students of human behavior marvel at the miracle of speech. The majority of us just take it for granted.[1]

Usually, if a child does not have adequate speech by the age of 4 years, he should be referred for help. Sometimes this should be done earlier. Children do not outgrow speech difficulty. Children in the 2-to-3-year age range will often mispronounce words in their process of learning to talk, but this learning procedure is perfectly normal. However, the child of 4 years and older with deviant and often unintelligible speech has a speech problem which is not outgrown. The common fallacy that children outgrow their errors, which is still believed by many physicians, has long been disproved by numerous studies in the speech field. If a child has a definite speech problem, it becomes more set in his habitual speech pattern as he grows older. When he enters school he is often ridiculed and teased by other children, and this in turn brings emotional problems which could have been avoided. The child suffers from profound feelings of inferiority and shyness and withdraws from social contacts. He may become depressed and sensitive and may adopt socially unacceptable behavior to compensate for his deficiencies in speech. Most speech disorders could probably be prevented if children did not have to learn the most difficult of all human coordinations with little help and much interference. Most of us do learn to master the art of speech. Speech therapists, however, who deal with speech-defective children and adults recognize the wonderful achievement involved in learning to talk.[1]

CLASSIFICATION OF SPEECH PROBLEMS

Delayed Speech.—A child's speech may be considered delayed if he has

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none or very few words by the age of 3 years. Usually by this age his sentence pattern is already established or he is putting two or three words together. Causes of delayed speech may be lack of motivation, improper learning, emotional conflicts, neuromuscular impairment, aphasia, mental retardation, or hearing loss.

These children should be referred to a speech specialist as early as possible. Most physicians are reluctant to refer a 3-year-old child for speech help. However, the majority of these children do not need any training at this age, but often the parents, after one interview, can learn to provide a better speech environment for the child, giving him more motivation and stimulation so that he will make an effort to learn to talk.

The possible causes of delayed speech in the normal child with no organic defects often become apparent after close observation. The child may not have any association with other children, or the parents, by striving for perfection, may discourage early speech attempts. The mother may put too much pressure on the child to talk and make too many demands upon his speech. Sometimes older siblings talk for him and announce his needs so often that he feels no incentive to speak for himself. His wants are often anticipated by parents who rush to the child the moment he grunts and points to the desired object. Children talk out of their need for language.

The pediatrician must use his judgment in referring these children, but many problems can be avoided and parents' anxieties lessened if they are referred early.

Articulation.—Articulatory disorders consist of substitution, omission, and distortion of sounds, caused by organic abnormalities, motor incoordination, emotional conflicts, mental retardation, and improper habit patterns. Children with defective articulation should be referred for speech therapy by approximately 4 years of age. This is, of course, flexible, since certainly a 4-year-old child with extremely deviant articulation and unintelligible speech, who is becoming sensitive and frustrated by his inability to communicate and may already be teased by other children, should be referred earlier than a 5-year-old child, for instance, who has very few distortions and is not at all sensitive about his speech.

One of the first steps the speech therapist takes in articulatory disorders is testing the younger child by means of pictures and the older one by oral stimulation or sentences. A phonetic analysis is used to determine the nature, number, and characteristics of the articulatory errors. Stimulation is vital in determining which sounds will be easily mastered.

Therapy is presented through games and techniques at the child's level so that speech becomes enjoyable. General procedures are to: (1) present adequate language stimulation through reading, games, activities, and associated experiences; (2) eliminate or minimize the effect of factors causing the defect; (3) create vivid auditory impressions which will enable the child to recognize readily both the error and the correct sounds, and to discriminate between the two whenever he hears them; (4) teach correct production of the sounds in isolation; (5) strengthen the correct production of the sounds so that they can be produced easily and voluntarily; (6) secure transfer of the correct sounds into connected speech in a small nucleus of commonly used sounds and words; (7) make the production of the correct sounds, instead of the error, habitual in all connected speech.[2]

Voice Disorders.—Isolated voice problems in children are not very frequent. Many voice disorders are medical problems and should always be first referred to a competent otolaryngologist However, many voice problems accompany other difficulties such as cleft palate nasality. Generally speaking, most cases of voice problems in children will deal with the aforementioned hypernasal voice quality of the cleft palate; throaty, guttural, or harsh voice of the cerebral palsied; and monotone or peculiar inflections of the deaf child. Causes of voice disorders in children might be a hearing loss, delayed sexual development, puberty, sluggish articulators, strain, hypertension, imitation, or emotional maladjustment.

The voice quality of a child with a hearing loss often gives us a good clue as to the severity of the loss.

Treatment will vary with the individual child, and these children should be referred for speech help at the various times discussed under their individual classification.

Stuttering.—Stuttering is a disorder characterized by blocking, prolongations, and repetitions of words, syllables, or sounds, usually caused by emotional problems.

When a child is first regarded as a stutterer, the only observable reactions are short, effortless prolongations or repetitions. The child is at first unaware that there has been any interruption or nonfluency. Sooner or later, however, this period of nonreacting acceptance is disturbed. Parents, teachers, or playmates react emotionally or call attention to the speech nonfluencies, and the child becomes aware of the fact that his manner of speaking is not acceptable to others and interferes with his communication. He is labeled a stutterer and becomes aware of his repetitions or hesitations. Behavior indicative of this awareness soon appears. The once unnoticed repetitions are followed by blocking and sudden pauses. The child begins to force the speech attempt, and tension and fear develop which soon become habitual symptoms.[3] Soon we have the secondary phase of stuttering. To some degree, and with variations from case to case, in time there are likely to be increased tension of the chest and mouth musculature, interference with the breathing pattern, social and emotional maladjustment, and symptoms of avoidance, postponement, antiexpectancy, starters, release, and disguise.

During the early nonfluent years, the pediatrician can give the parents many helpful suggestions along the lines of never calling attention to the interruptions in the child's speech, never asking him to slow down or start over, making the child feel that his interruptions are normal and perfectly acceptable, not labeling him a "stutterer," giving him ample opportunity to speak, and avoiding situations which are unduly frustrating, exciting, bewildering, tiring, humiliating, or frightening to the child.[4]

If, by the age of 5 years, the child is still blocking, repeating sounds or syllables, or hesitating, he should be referred for speech help, or sooner if the parents' anxieties grow or the child shows some of the aggravated reactions discussed previously.

Cleft Palate.—Cleft palate speech is characterized by both articulatory and voice defects. Much can be done for the cleft palate child either surgically or through prosthesis. Prosthodontia has gained an important place in the rehabilitation of the cleft palate. Surgically, various operative techniques are used to close the open cleft and lengthen or readjust the muscular tissue or velum. The parents should be directed to a speech therapist six months after surgical repair for various postoperative speech techniques, but regular training often does not actually begin until a later age. The aims of treatment are to strengthen the muscles of the soft palate and those involved in the velopharyngeal closure, to teach the child to effect a better velopharyngeal closure and to direct the air stream through the oral opening, to increase the mobility of the tongue, lips, and other articulators, and to teach or correct articulation.

The main problem of speech re-education is that of training the patient to close the opening into the nose voluntarily by drawing the velum upward and backward, and constricting the pharyngeal wall to meet the velum.[5] Incorrect tongue and lip positions in the various consonant sounds are the natural result of compensatory movements of the articulatory apparatus before palatal reconstruction has been provided. The postoperative cleft palate patient must, therefore, be guided into correct articulatory patterns.

He must prevent overelevation of the dorsum of the tongue, keep the tensions in the pharynx at a minimal level, and phonate effectively.

Cerebral Palsy.—The diagnosis of cerebral palsy is the province of the physician. Since cerebral palsy is a neuromuscular handicap, it often affects muscles used during the act of speaking. More than 70 per cent of all cerebral palsied children will have speech difficulty. Usually, they should receive their speech therapy in conjunction with occupational or physical therapy if needed, or in conjunction with their educational program. There is no such thing as typical cerebral palsy speech. The cerebral palsied child presents individual problems of delayed speech, voice disorders, articulation diffculty, breathing problems, and the like. The therapeutic program is usually divided into a physiological approach and one of language stimulation. Since speech is an overlaid function, the muscle action used during the act of speaking as in chewing, swallowing, or sucking, must usually be improved. Often these youngsters are kept on a soft strained food program too long, and have later difficulty in chewing and also in speaking.[6]

We have to take into account all of the frustrations that a handicapped child experiences which hinder language development. The normal child can explore his environment with his eyes, ears, head, hands, feet, and even his mouth with far greater ease than can the motor-handicapped child. These experiences became part of the language atmosphere of the child, and that is why a great portion of speech therapy must deal with language stimulation.

Hearing Loss.—The language element must be given priority over any other in the training of the deaf or hard of hearing child. Possible characteristic signs that mark a hearing loss in young children are changes in voice quality, consistent ignoring of verbal directions, behavioral changes, lack of understanding, frequent requests for repetition of questions, close observation of the face of parents or others while talking, turning up the radio, phonograph, or television, and lack of response to household and other sounds occurring around him.

Before a child with a suspected hearing loss is referred to a speech therapist for training or testing, he should first be referred to a competent otolaryngologist for an ear, nose, and throat examination.

If needed, auditory training and lip reading instruction should begin as soon as possible, and, more important, a program should be worked out with the parents so that there can be complete cooperation between the parents, the therapist, the teacher, and the doctor, to give the child every possible opportunity of effecting better communication.

TRAINING FOR SPEECH PATHOLOGY

It may be helpful for the pediatrician to know what constitutes training for speech pathology. The American Speech and Hearing Association has drawn up rules of Clinical Certification requirements which can be referred to.[7]

SUMMARY

The training and function of speech pathology are discussed, with emphasis placed on classification, proper time of referral, etiology, and treatment techniques of common speech disorders.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS male infant was referred to The Children's Medical Center at 2 hours of age because of an imperforate anus. His gestational period was without incident, the delivery was uneventful, and initiation of respiration was prompt. The birth weight was 7 pounds 5 ounces.

On admission to the hospital the infant exhibited cyanosis of the circumoral areas, hands, and feet. The chest was clear and the heart was not remarkable. His abdomen was soft and not distended. He had an imperforate anus, with a band of tissue overlying the area; this was seen to contract on local stimulation. Slightly lateral to this band was a fistulous tract. The remainder of the physical examination revealed no abnormalities.

The laboratory examinations revealed a hemoglobin of 21.0 Gm. per cent and 24,000 leukocytes per cubic millimeter in the peripheral blood. A urinalysis on the third hospital day showed pH 5.0, albumin 7.5 mg. per liter, erythrocytes 8 to 10, and leukocytes 10 to 20 per high-power field. A chest roentgenogram was normal. In the film of the abdomen there was gaseous distention of the distal bowel, the nearest approach of the gas to the anal dimple being 2.5 cm.

On the second hospital day, a perianal anoplasty was performed and a rectourethral fistula excised. Tetracycline was given. His oral fluid intake in the immediately postoperative period was 12 to 14 ounces per day. On the fourth postoperative day, he had diarrhea with ten loose watery stools, and this continued for two days. On the fifth postoperative day, his indwelling catheter was removed and he was voiding well. Because of poor oral intake on the eighth postoperative day, he was given intravenous fluids for one day; he had lost 1 pound 7 ounces from his birth weight. Ten days after operation, urine output ceased and six hours later bleeding from both urethra and rectum were noted. Stool cultures taken at this time grew *Staphylococcus aureus,* gamma Streptococci, and *Bacillus proteus.* His pulse at this time was 160, his hemoglobin 14.0 Gm. per cent. He was given vitamin K and 35 c.c. of whole blood. Six hours after the bleeding was first noted, there was a sudden onset of dyspnea and cyanosis. Physical examination at this time revealed respirations 60 per minute, pulse 172, and temperature (axillary) 94.0° F. Breath sounds were transmitted well but the heart sounds were distant. A bedside roentgenogram showed the heart to be slightly enlarged, but no abnormality of the lungs could be detected. The carbon dioxide content of the serum now was 9.3 volumes per cent and the chlorides 113.5 mEq. per liter. Despite resuscitative measures the infant died 45 minutes later.

DISCUSSION

DR. DAVID GITLIN.*—I wonder if I could ask if this bleeding episode on the last day of life was actually blood, or was it serosanguineous, or was it mixed with blood?

DR. CRAIG.—The baby hemorrhaged a "large amount" from the rectum and there was also a large amount of grossly bloody fluid passed from the urethra.

DR. GITLIN.—Well, that is very helpful. The hemoglobin at the time of the bleeding episodes was 14 Gm.; the baby came in with 21 Gm. of hemoglobin and a normal white count for a baby 2 hours of age. In view of the fact that the baby had had considerable sudden weight loss, reflecting serious dehydration, I would have expected the hemoglobin to be a bit higher than 14 Gm. The pulse was 172 per minute at that time, which is rapid even for a newborn infant. It would appear that the baby was in shock. The heart sounds were distant, but it is possible that the child had an interstitial myocarditis or that the myocardium was otherwise damaged.

In going over this protocol, I was struck by three things: one, the manifestation of asphyxia in the presence of lungs that were perfectly clear; two, the distant heart sounds; and three, and most important, the passage of gross blood from the rectum and the urethra.

With respect to the bleeding from the urethra and rectum seen at eleven days of age, one would not ordinarily expect bleeding internally from a simple anoplasty since the sutures are at the skin surface in this operation. Therefore, the origin of the bleeding was an area away from the operative site. It occurred ten days after the operation and I would have expected the operative wound to have healed long before this time. If the wound were to break down, it would have done so earlier than ten days postoperatively.

If this bleeding was not related to the operation, what disease process would cause bleeding from the urethra and the rectum at the same time? Two possible causes are prominent in my thinking about this case. The first is bilateral renal cortical necrosis. Most of the cases with this condition that have been described were associated with diarrhea, sepsis, severe dehydration, and acidosis. Pulmonary edema and hemorrhage have been notable. Pulmonary edema was not present here, but the other factors were: severe dehydration, acidosis, diarrhea, and infection. Can renal cortical necrosis kill so quickly? Well, we do not know, actually, how long this condition might have been present. We do know that the child was anuric for the last twelve hours of life. We do

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not know whether the baby was oliguric, nor what the urine showed before this time, so we have no real way of knowing exactly when this renal process might have begun. It could have started several days before death, with manifestations of albuminuria, casts, and minimal hematuria. In bilateral cortical necrosis, arteries and small artery thrombosis occur, and in some of the cases that Dr. Zuelzer reported[1] the smaller branches of the superior mesenteric artery were involved with the development of infarction and gangrene of the upper intestine, resulting in melena. I am unhappy about the short duration of obvious difficulty with relation to a diagnosis of bilateral renal cortical necrosis, but it is possible. Most children with this condition are anuric for at least twenty-four hours, and apparently succumb within one to five days after the onset of the disease. With proper fluid therapy, some of these children may be kept alive for some days, yet others have died within two days, or less, of the onset.

The second possibility which I believe may be invoked as cause of the renal and urethral bleeding is bilateral renal thrombosis. It is impossible for me to differentiate, clinically, between bilateral renal vein thrombosis and bilateral renal arterial thrombosis. Dr. Zuelzer described cases of bilateral renal thrombosis which, clinically, were identified with those referred to above —with passage of blood via the rectum and the urethra.

There is a question here as to whether or not the rapid heart rate and weak sounds were due to myocardial damage. Does myocardial damage occur with bilateral renal cortical necrosis? Myocardial damage is common in acute glomerulonephritis, though it may not be histologically detectable; so here too, a weakening of the myocardium due to acute renal involvement may be present. Since this child did have an imperforate anus, a second congenital anomaly might possibly be considered to have been present in the child, but there was no indication of congenital heart disease.

Sepsis frequently is associated with the onset of bilateral renal cortical necrosis; we do not know whether sepsis was present or not.

The question of the importance of staphylococci or the coliform group in such cases arises. In the newborn period, it is always wise to remember that, statistically, the organisms most frequently involved in any case of septicemia or bacteremia are of the coliform group. Yet, here I believe that staphylococci caused all the difficulty since bilateral renal cortical necrosis has been almost universally associated with a staphylococcal septicemia.

This child may have died of a pulmonary embolus secondary to venous thrombosis, yet if such were so, I would have expected the child to die much more quickly. On physical examination, however, no abdominal masses suggestive of enlargement of the kidneys were found, which is an argument against the presence of renal vein thrombosis.

In summary, I believe this infant had multiple thromboses, primarily of an arterial nature, involving the kidneys and the superior mesenteric artery. I expect that the pathologist may report some evidence of myocardial damage. I cannot rule out the presence of sepsis, or of cerebral venous sinus thrombosis.

DR. NICHOLAS STAHL.—I would like to ask Dr. Gitlin, if multiple arterial emboli and thromboses were present, would he not expect to find additional thromboses in the limb vessels with the appearance of gangrene?

DR. GITLIN.—It is possible to have involvement of the superior mesenteric artery and the renal arteries, particularly an arteritis with thromboses in the smaller branches without involvement of the peripheral circulation. There is a case, however, that Dr. Zuelzer does describe in which there was massive thrombosis of the aorta from an embolus, arising in the ductus arteriosus with infarction of the kidneys and early gangrene of several toes.

If such were the case here, I would have suspected that perhaps the peripheral circulation would be compromised. No description of peripheral pulses or the appearance of his extremities was given in the protocol.

DR. NADAS.—I would agree with Dr. Gitlin that this baby probably did not have congenital heart disease. I do not believe that this child had heart disease at all. The heart sounds arise from the slamming shut of valves, the first sound coming from the closing atrioventricular valves. If the ventricles do not contract efficiently, your first heart sounds will be of low intensity. The second heart sound, in essence, is a slamming of the semilunar valves; and if there is cardiac failure or a poor pressure generated in the ventricles and there is not a very good gradient in diastole between artery and the ventricle, again, the door will not be slammed so forcefully. Another cause of poor heart sounds may be shock. Weak heart sounds, then, imply a general ineffectiveness of the circulation, either starting from the periphery or starting in the heart itself.

DR. R. CANNON ELEY.—One wonders, with bleeding described in two areas (the bowel and the urethra) what the peripheral blood platelet level was? Might there not also have been bleeding into the myocardium or in the pericardial sac to account for the change in the heart sounds?

DR. LOUIS K. DIAMOND.—I believe no petechiae or ecchymoses were described to suggest a decrease in platelets.

DR. MARTIN H. WITTENBORG.—On the day of admission, the patient had chest, abdomen, and "upside down" films. The "upside down films" are not directed at making the diagnosis of imperforate anus but are an attempt to see the actual distance between the anal dimple and the obliterated colon. If that distance, best shown on a lateral film, exceeds a certain length, the operation becomes technically more difficult. The chest was normal at the time of admission. The heart was top normal in size, by our estimate.

DR. FARBER.—Dr. Gitlin, with your permission could I just summarize what you have said?

You assume here that the congenital malformation which was corrected surgically was just an event in this child's life, which had, in all likelihood, nothing to do with subsequent events. Then, you looked elsewhere for explanation of the blood in the urine and from the rectum; either you were dealing with a *locus minoris resistentiae* or you were dealing with the effect of infection, with a bilateral symmetrical cortical necrosis of the kidneys, giving the hemorrhage into the bladder, and you looked for thrombosis of some of the mesenteric vessels to account for hemorrhage into the rectum. You suggested, also, the possibility of infection and dehydration together, causing thrombosis on the venous side, including the dural sinuses and veins elsewhere in the body, and hemorrhage explained by involvement of thrombosis, in the kidneys perhaps. And, finally, you mentioned thrombosis of the renal arteries, causing very massive infarction of the kidneys. If you suggest that, you also suggest involvement of mesenteric vessels to account for the bleeding.

DR. JAY BERNSTEIN.—The major finding in this case was "thrombosis of the aorta" which involved the renal, the superior mesenteric, and the celiac arteries (Fig. 1). This thrombus was adherent to the intimal surface of the aorta, although there was no microscopic evidence of organization. Apparently the source of this thrombus was an embolus from the ductus arteriosus. This vessel contained a thrombus within its lumen which protruded into the aorta (Fig. 2). This thrombus in the ductus was friable, and, presumably, pieces of it could have broken off and caused the embolization which occurred peripherally. On microscopic examination of the ductus there was no good reason for the formation of this thrombus; the thrombotic material occupies the lumen and there is no organization of it, and the intimal surface of the ductus is thickened in an irregular sort of way, which is not an infrequent finding in otherwise normal ductus arteriosus.

The kidneys, as a result of the occlusion of the aorta and renal arteries, were almost entirely infarcted, with a broad central zone of necrosis, peripheral hemorrhagic zone, and a nearly intact subcapsular zone. Several small thrombi were present in some of the renal vessels, which appeared to be of various ages. This led us to suspect that the embolization occurred over a period of a few days, which might account for the urinary findings a few days before death. In the gastrointestinal tract, where the small arteries were involved, there was a good deal of congestion, and in association with that there was edema of the submucosa and some extravasation of blood, but most of the damage was to the mucosa, indicating that the ischemia was partial, causing a hemorrhagic lamina propria. These small emboli also were present in the small arteries of the testes and the periadrenal arteries, causing an infarctive necrosis of the adrenal cortex. Bacteria grew in great profusion on the mucosal surface of the intestine and we cultured coliform organisms from the intestine, the heart, and the lung, so that a generalized sepsis was present. Many small foci of bronchopneumonia were present within the lungs.

DR. FARBER.—Another explanation in some cases with simultaneous thrombosis of the ductus arteriosus and the bifurcation of the aorta may pertain. The umbilical arteries, which undergo degenerative changes during involution shortly after birth, may become thrombosed if the process of involution is

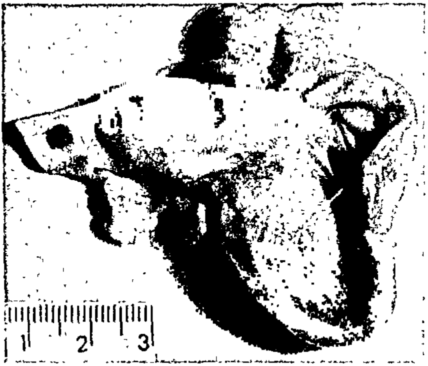

Fig. 1.—Heart. The ductus arteriosus contains a thrombus which protrudes into the lumen of the aorta.

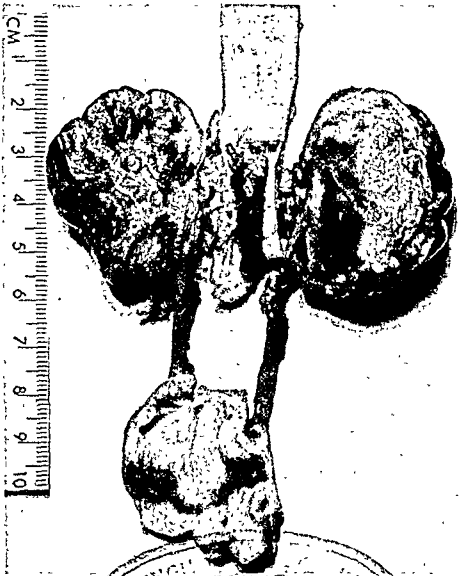

Fig. 2.—Kidneys, ureters, bladder, and aorta. A large thrombus extends from the celiac axis to the bifurcation of the aorta. Both kidneys have an extensive hemorrhagic infarction.

SAWAI [illegible] SINGH LIBRARY

hastened or exaggerated. The thrombus arising here may undergo retrograde spread into the iliac and aortic vessels. The extension and location of the thrombus will then determine the extent of the damage; a saddle thrombus may cut off the blood supply to one or both legs, with a resulting gangrene. There may be further retrograde progression up the aorta so that infarction of the adrenals or kidneys may occur. The clinical picture will be determined by the distribution and extent of the thrombosis.

In other cases there has been embolization from a thrombus in the ductus to both the pulmonary and the systemic circulation with infarction of the lung as well as the brain and other portions of the body.

In many cases, the ductus arteriosus may contain thrombi in which no embolization occurs and may be associated with an aneurysmal dilatation of the ductus. In other cases there is a minor thrombotic accumulation of material on the intimal surface, but again no embolization.

DR. STAHL.—Were these cases associated with dehydration?

DR. FARBER.—No, dehydration was not an important part of the picture.

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Medical Progress

RECENT APPROACHES TO THE BIOLOGY OF SCHIZOPHRENIA

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RECENTLY there has been a resurgence of interest in the biochemical and neurophysiological approach to schizophrenia. Reports have appeared in the literature of biochemical tests which are positive in schizophrenia and of studies relating epinephrine, serotonin, and other physiological substances to the production or remission of induced psychotic reactions.

Opinion as to the meaning of these studies varies. Some appear to hold the point of view that a specific etiological agent in schizophrenia has been identified, while others feel that there is no basis for assuming any metabolic factor in this illness. Actually, the controversy about the etiology of schizophrenia began when Kraepelin first described dementia praecox at the turn of the century. While there has been considerable advance in knowledge during the intervening period, we are still unable to evaluate the relative importance of exogenous and endogenous factors as causative elements. Today, the general trend appears to be toward emphasizing the interaction of innate predisposition and environmental stress.

It seems quite possible that all cases of schizophrenia do not develop in the same manner. While the etiology and pathogenesis of schizophrenia remain speculative, it nonetheless seems reasonable to assume that the marked psychological and behavioral changes in the schizophrenic are mediated either through altered biochemical mechanisms or patterns of physiological organization. Whether these biological aberrations are inborn and primary or are secondary to emotional trauma, it seems likely that they must nevertheless play an important role in producing the symptoms of this illness.

Many studies have been made of the biology of schizophrenia, and these are dealt with in a number of excellent texts and reviews.[1-5] Some of the more recent studies will be considered here in an attempt to present the status of work in several areas that have attracted widespread interest.

LABORATORY TESTS FOR SCHIZOPHRENIA

Because of the subjective nature of the symptoms of mental illness, there is frequent disagreement in the diagnosis of schizophrenia. This has led to difficulties in establishing comparable groups of schizophrenics for research purposes and also to a lack of uniform criteria for therapeutic and prognostic application. As a result, many efforts have been made to establish a laboratory test to differentiate

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the schizophrenic. Frequently, such work is begun as an investigation of biochemical differences. When the procedures are reasonably simple, attempts have often been made to adapt them as tests.

The recent work by Akerfeldt[6] in Sweden developed in this manner. He has been determining the effects of serum from schizophrenic patients and from the normal population on paraphenylene diamine. He found that when the N,N-dimethyl form of this substance is added to serum, the paraphenylene diamine becomes oxidized and turns a red color. The increase in intensity of red coloration can then be measured spectrophotometrically. In his series Akerfeldt found that the schizophrenics had significantly higher results than did the normal controls. Others have confirmed Akerfeldt's findings and have reported that about 80 per cent of the schizophrenic group have positive reactions, as compared to 3 per cent of the normal group. However, positive results are also found in a large percentage of patients with other conditions, including liver disease, neoplasm, and pregnancy in the last trimester.[7]

Akerfeldt's work was based on findings in Germany in 1941 that serum copper levels were elevated in schizophrenia,[8] and also on the isolation by Holmberg and Laurell[9, 10] in 1948 of a substance in the serum known as ceruloplasmin. This substance, which is found in the alpha globulin fraction, contains most if not all of the serum copper.

Paraphenylene diamine is known to be a substrate for ceruloplasmin, which is believed to oxidize the amine enzymatically to a red-colored compound. The color reaction, however, is dependent not only on the oxidation of paraphenylene diamine by ceruloplasmin, but also on its inhibition by various reducing substances found in the serum. Some of these have been identified as ascorbic acid and certain sulfhydryl compounds.[11]

The curve obtained in the test is the net result of various substances acting in concert (Fig. 1). The lag period before the initial rise is believed to be due to the influence of ascorbic acid and increases in length as the ascorbic acid concentration increases. The maximum slope of the curve apparently represents the maximum oxidizing effect of ceruloplasmin, whereas the bend of the curve from the linear is thought to represent the effects of sulfhydryl compounds.

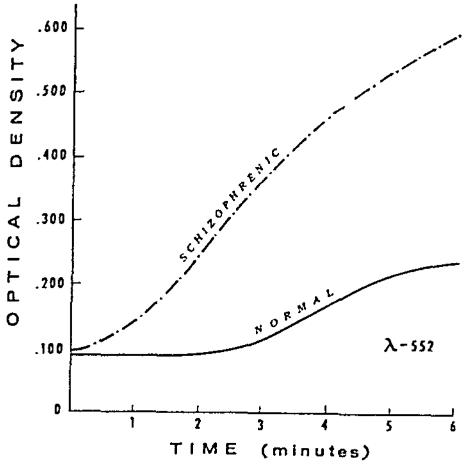

Fig. 1.—Typical curves obtained from the oxidation of N,N-dimethyl paraphenylene diamine by normal and schizophrenic serum.

Akerfeldt found that the lag period in the schizophrenic group is shorter (low ascorbic acid level), that the maximum slope is greater (high ceruloplasmin level), and that the bending of the curve away from the linear is more marked (high level of sulfhydryl substances).

Low ascorbic acid levels have also previously been reported in schizophrenia.[12] Here, however, the possibility of nutritional differences must be eliminated. In an attempt to control this factor, patients and normal controls were given fixed quantities of ascorbic acid for six days, with the finding that ascorbic acid did not diffuse out of the serum as rapidly in schizophrenics as in normal persons.[11]

It has also been demonstrated that feeding large quantities of ascorbic acid to schizophrenic patients increases the length of the lag period and changes the results of the paraphenylene diamine test toward normal, but without evidencing any therapeutic effects on the patients.[13]

Ceruloplasmin, which is believed to be the oxidative enzyme functioning in the Akerfeldt reaction, is also active against other substrates. Among these is epinephrine. Although there is no evidence that such an action occurs in vivo, significant statistical differences in the oxidation rate of epinephrine in vitro in schizophrenic serum have been reported.[14]

In the course of extracting ceruloplasmin from schizophrenic serum, Heath[15] at Tulane prepared a substance called taraxein which he reports causes schizophrenic-like symptoms in normal volunteers. A similar preparation from the serum of normal individuals did not cause these symptoms. Confirmatory evidence of these findings from other laboratories have not yet been reported.

Other abnormalities in schizophrenic serum and urine have been reported by a number of different investigators.[16-21] One recent study indicates that glyoxylic acid is present in the urine of the majority of schizophrenics tested, whereas it is absent in the majority of the nonschizophrenic group which included other psychiatric patients and normal controls.[22] The best-controlled of these studies appears to be one by McGeer and associates,[23] who found abnormal spots by chromatography in schizophrenic urine. They also found that these abnormalities could be corrected by withholding tyrosine and phenylalanine from the diet.

In all of these reported studies there has been overlapping in results between the schizophrenic group and the normal or nonschizophrenic group. To qualify as a test, a high degree of specificity is desirable. Furthermore, none of these studies have yet been adequately controlled from the dietary and other standpoints.[24] The Akerfeldt procedure, for instance, can be profoundly influenced by ascorbic acid intake and perhaps by other unknown factors more related to hospitalization than to schizophrenia.

While the report of a psychotogenic factor in schizophrenic serum has been considered here because of its relation to ceruloplasmin, the nature of this substance does not make it possible to use it as a test. Perhaps each of these findings is much more important as a lead in the search for metabolic concomitants of mental illness. We can say that at the present time there is no laboratory test for schizophrenia, although many of the studies reported could well be the first step in the development of one.

SEROTONIN IN MENTAL ILLNESS

Although serotonin has been known as a potent constrictor of smooth muscle for some time,[25] only within the past few years has it become associated with mental functioning. Two nearly concurrent findings stimulated the study of its possible relationship to psychoses. First, it was discovered that serotonin's constrictive action could be antagonized by a minute quantity of the hallucinogen lysergic acid (LSD).[26] Second, serotonin was found to be a normal constituent of brain tissue,[27] particularly in the hypothalamic region and the area postrema.[28]

Since it had been known that LSD, in quantities as low as 1 mcg. per kilogram, could induce psychotic behavior in some ways similar to that of schizophrenia,[29, 30] it was logical to speculate that the psychotogenic action of this hallucinogen might be the result of its inhibitory action on serotonin. If it could be demonstrated that all substances which counter the effects of serotonin also produce psychotic symptoms, this would suggest that serotonin mediated some psychotic reactions.[31] While it was found that some antiserotonin substances did, in fact, act similarly to LSD, a close relative of this substance, brom-LSD, proved to be one of the exceptions.[32] Although it was a more potent antagonist of serotonin than LSD, it did not produce psychotic symptoms. Clearly, then, it was necessary to investigate the serotonin in the brain.

Such a study was initiated by Woolley at the Rockefeller Institute with the cooperation of Drs. Murray and Benitez of Columbia University.[33] Through the use of time-lapse films, they showed that serotonin has a contractile effect not only on certain smooth muscle, but also on the oligodendroglial cells of the central nervous system. Woolley suggests that these contractions, though admittedly slow and occurring somewhere in the range of one every five minutes, produce a kind of stirring action which may be important for brain circulation. However, when LSD was tested on serotonin-induced contractions of oligodendroglia, its effects were found to be less straightforward than those on smooth muscle.

The question that now arises is why serotonin has not been studied through direct injection in human subjects. The difficulty with this approach is that serotonin does not penetrate the blood-brain barrier in any appreciable quantity,[31] and that large doses produce marked effects on the cardiovascular system.[34]

Other ways, however, have been utilized to determine the effects of serotonin in increased concentrations. One method is based on the finding that 5-hydroxytryptophan, a precursor of serotonin, when fed to rabbits or dogs passes the blood-brain barrier and increases the level of free serotonin in the brain.[35] This increase is reported to produce an LSD-like effect in rabbits.[36]

Another method makes use of the knowledge that serotonin is metabolized by the enzyme, monoamine oxidase.[37] Since iproniazid is known to be an inhibitor of monoamine oxidase,[38] administration of this drug is thought to increase the level of brain serotonin by inhibiting its destruction. A clinical application of this principle has been made by Kline[39] with good results in a series of chronically depressed patients who were given iproniazid over a period of several months. In this instance, the presumably high levels of serotonin were therapeutic.

An interesting explanation has been proposed which relates the effect of the tranquilizer, reserpine, to its action on brain serotonin.[40] Serotonin is believed to occur mainly in the bound form in the brain, and reserpine appears to act by liberating it. The result is a depletion of the store of bound serotonin and a temporary increase in free serotonin. However, since free serotonin is readily metabolized by monoamine oxidase, the ultimate effect of reserpine is a decrease of both the bound and the free forms, thus depleting the total content of brain serotonin. Reserpine is thought to act by impairing the binding sites for free serotonin, which is apparently the pharmacologically active form,[36] thereby causing a persistent low concentration. It is this persistent low level of free serotonin that is believed to be responsible for the effects of reserpine. It is perhaps of more than passing interest that an occasional side effect of reserpine action is the production of depression.[41]

At present there is no clear evidence for assigning to serotonin a role in the normal or abnormal functioning of the brain. However, some intriguing possibilities are suggested by the large concentration of serotonin in the hypothalamus of both animals and human beings, and by the response of brain serotonin to reserpine ingestion. The relationship of serotonin to the action of hallucinogens such as lysergic acid is as yet unclear.

One interpretation of the work on this substance suggests that a low level of brain serotonin might be related to depression or tranquilization. From this point of view, an excessively high level of serotonin produces an effect similar to that created by hallucinogens such as LSD. However, a contrary view is that low levels of serotonin produce psychotic symptoms and high levels have a therapeutic effect. Further work is necessary to clarify this point.

EPINEPHRINE AND NOREPINEPHRINE

Epinephrine has long been familiar to every physician. It may be surprising, therefore, that its metabolism and detoxification remain at present poorly understood, though a number of possible pathways have been suggested for its rapid destruction. Its function in the central nervous system is obscure and it is not clear whether any of the epinephrine secreted by the adrenal medulla passes the blood-brain barrier. However, because of the observation that epinephrine is secreted as a result of various stresses,[42] persistent efforts have been made to relate this substance to mental illness. Attempts to measure blood levels of epinephrine in psychiatric patients[43] are not conclusive, primarily because of technical problems involved in measuring epinephrine which is normally present in only minute quantities.

It is now believed that norepinephrine is the major secretion of the resting adrenal medulla.[44-46] Norepinephrine secretion is apparently increased in aggressive reactions, while epinephrine secretion is increased in anxious withdrawal. Studies on psychotic patients suggest that these patients maintain either one or the other of these reactions and, in contrast to normals, are unable to return to their resting level of function after stress.[47]

Inasmuch as the metabolic pathways for the destruction of epinephrine are not clear, this has led to a great deal of speculation that abnormal products of epinephrine degradation might be responsible for the symptoms of schizophrenia.[48]

Adrenochrome, a pink substance resulting from the partial oxidation of epinephrine *in vitro, was discovered in* 1948.[49] Considering the possibility that epinephrine oxidation might also take place in vivo, Hoffer and his group[50] in Canada prepared adrenochrome and injected it in a series of subjects, reportedly producing hallucinations and other psychotic manifestations. Unfortunately, however, these investigators were unable to repeat their work, and others have not verified their findings.[51] Further studies led to the speculation that adrenolutin, another product of Adrenalin oxidation, might be responsible for psychotic symptoms, rather than adrenochrome.[52] The difficulty to date, however, is that neither of these substances have been found in vivo, nor is there any real evidence that they play any role in the production of schizophrenia.

It is of interest, nevertheless, that norepinephrine has been found in the brain in large concentrations in the hypothalamus,[53] the same region where concentrations of serotonin are high. Recent studies demonstrate that reserpine decreases the concentration of brain norepinephrine in the same manner as it does brain serotonin.[54] It is possible, therefore, that norepinephrine may also play a part in the therapeutic effects of reserpine in schizophrenia.

At present, however, only circumstantial evidence exists to relate disturbances in the sympathetic nervous system, or in the function of the adrenal medulla, to schizophrenia or other forms of mental illness.

CONCLUSIONS

The results emerging from interest in biological research on schizophrenia are in an early and tentative state. It is well to bear in mind when evaluating reports of metabolic abnormalities in mental illness that seeming differences between schizophrenic and other groups may be the result of incidental variables such as nutritional status and state of ambulation. These factors assume a special importance in evaluating reports of different levels of various substances in serum and urine of schizophrenics. At this point, some pathways for research have been suggested. Conclusions as to the ultimate significance of many of the findings discussed here must await further studies and controls.

The fact that so little biochemical work has been done on children with schizophrenia is worthy of note. These patients might well provide opportunities to study metabolic defects at an early stage before compensatory mechanisms become prominent. Similarly, while many studies have been made on the psychological characteristics of the families of schizophrenics, no work has been done on their biochemistry. Each of the areas discussed here provides opportunities for study with these two groups.

I wish to express my appreciation to Mrs. Muriel Henderson for technical assistance in the preparation of this article.

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Comments on Current Literature

POLIOMYELITIS-LIKE ILLNESSES

WITHIN recent years a number of "*polio-like illnesses*" has been described: distinct clinical entities with manifestations simulating in many respects those of poliomyelitis. One of these, so-called benign myalgic encephalomyelitis, or acute encephalomyalgia (Akureyri disease, Iceland disease), has occurred in epidemic form: in Iceland during the winter of 1948-1949, with long-term follow-up studies on some of these patients reported recently[1]; in the eastern United States in 1950[2]; in Australia in 1951[3]; in London in the summer of 1955,[4] including an epidemic among the personnel of the large Royal Free Hospital[5]; in Berlin among British military personnel in the autumn of 1955[6]; and other recorded epidemics. Two more recent outbreaks in the United States, one near Washington, D. C. (1953),[7] and one in Florida (1956),[8] are described under the title, "Epidemic Neuromyasthenia." No viral agent has been isolated from throat swabs, fecal specimens, or blood; agglutination tests were essentially negative, and antibody studies using well-recognized viral agents were not revealing. However, in the case of the Maryland investigation, bacteriologic studies ". . . by means of stool isolations and serum agglutinations disclosed convincing evidence of acute infection of a high proportion of ill patients with enteric bacteria of the Bethesda-Ballerup group of intermediate paracolon organisms."[7]

That these organisms were merely coincidental "fellow travelers" is considered possible, or probable, by the authors, and that "the major disease complex was caused by an unknown agent presumably originating from the same source."[7] The designation, epidemic neuromyasthenia, is suggested as the most appropriate and least confusing one; the results of further etiologic studies and justification for this designation will appear in a forthcoming summary article.[9]

Most of these reports emphasize the difficulty on clinical grounds of differentiating such disease entities from poliomyelitis in children and young people, especially early in the course of the illness. Likewise, the diverse clinical manifestations associated with types of Coxsackie infection constitute a subject which has been under discussion for the past several years: pleurodynia, myalgia, herpangina, myocarditis and encephalomyocarditis, especially in young infants, and aseptic meningitis. In cases of encephalomyalgia and aseptic meningitis simulating nonparalytic poliomyelitis, Coxsackie viruses of group B have been incriminated with the isolation of virus from stool specimens, cerebrospinal fluid, and in fatal cases of encephalomyocarditis in infants, from brain tissue, spinal cord, and the myocardium. In an epidemic of aseptic meningitis in Minnesota, occurring in the late summer and autumn of 1956, Coxsackie B_5 was incriminated by antibody studies and by the isolation of virus from stool specimens of 61 acutely ill patients. A laboratory, clinical, and epidemiologic study of this outbreak was reported recently by Syverton and his associates.[10] On the other hand, group A Coxsackie viruses with few exceptions[11] have been thought to be

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suckling mice and in tissue culture against the Coxsackie A_7 strains which had been maintained since their isolation by Habel and Loomis. Tissue culture preparations inoculated with the Russian AB IV strain (original cotton-rat brain material) included HeLa cells, human skin epithelium, human fibroblasts and amnion cells, and monkey kidney epithelial cells. No cytopathogenic effect was detected except in monkey kidney epithelial cells, where, after an interval of from eight to ten days, a few scattered individual cells appeared to be round and refractile. While this slight degenerative effect was not progressive and did not extend over the cell sheet, it was definite and consistent, and was specific in that it seemed to be prevented entirely by AB IV and by Coxsackie A_7 antiserum. These results are similar to those obtained when cultivation of the Coxsackie A_7 viruses is attempted in tissue culture.

In view of the fact that the original isolation by the Russian investigators had been made from fecal specimens of patients acutely ill with clinical manifestations indistinguishable from those of poliomyelitis, and that typical polio lesions followed the inoculation of this material into monkeys, careful neutralization studies were necessary to rule out possible admixture of Coxsackie A_7 virus with poliovirus, or with some other neurotropic agent. These studies did not disclose the presence of other agents, and, in every test instance, the AB IV strain of virus was neutralized completely by standard Coxsackie A_7 antiserum, and never by antiserum against types 1, 2, or 3 polioviruses. The Russian workers had classified the strain AB IV as a possible "type 4 poliovirus" on the basis of the clinical paralysis observed in acutely ill children, because the strain was not neutralized by standard poliovirus antiserum to types 1, 2, or 3, and because the virus produced paralysis in monkeys with lesions in the central nervous system considered compatible with poliomyelitis in these animals. Habel and Loomis were able to confirm this pathologic picture in the central nervous system of infected monkeys. Certain of the inoculated monkeys showed changes in the central nervous system which were indistinguishable from those produced by the polioviruses, both in quality and in distribution. However, in some of the monkeys inoculated ". . . the lesions were distributed in . . . a manner that permitted differentiation . . ."[14] Lesions were observed in areas of the central nervous system rarely involved in infection with polioviruses: caudate nucleus, putamen, or both, and definite but minimal involvement of the hippocampal and the occipital cortex. "The equal degree of involvement of the motor (precentral) and of the anterior parietal (postcentral) cortex also was helpful in the differentiation."[14] Thus the pathogenesis of the AB IV and the Coxsackie A_7 viruses in the central nervous system appears to be essentially similar. No inclusion bodies could be demonstrated.

At the request of the authors, dilution passage viruses, both suckling mouse and tissue culture passages, were tested by Dr. Albert Sabin for monkey pathogenicity by intraspinal inoculation. Dr. Sabin reported ". . . that although no definite clinical paralysis developed in these animals, they showed poliomyelitis-like lesions with a distribution different from poliovirus infection."[14] While these investigations were in progress, the "type 4 poliovirus" isolated by the Russian workers was being studied also by Dr. Torsten Johnsson at the State Bacteriological Laboratory at Stockholm, who likewise identified the strain as a Coxsackie A_7 virus.

In a well-rounded discussion summary the authors state that the Coxsackie A_7 strains of virus are prevalent in the United States, and that the Russian investigators did not have specific Coxsackie virus typing serum available at the time that the AB IV strain was identified as a possible "type 4 poliovirus." The authors go on to say, "The findings of the Russian virologists, confirmed here, add one more facet to the broad spectrum represented by the Coxsackie, poliomyelitis, and certain Echo viruses where the properties of one group blend sometimes rather extensively with those of the others, and all seem capable of causing related and sometimes identical clinical and histological manifestations in experimental animals and man. Certainly our present knowledge of these relationships should emphasize the necessity of search for these other viruses in paralytic cases where the specific etiology of poliovirus cannot be established." ". . . Furthermore, the results reported here make it desirable that more extensive studies than those thus far reported be carried out with Coxsackie viruses in monkeys and chimpanzees to determine whether these characteristics may be found in types other than A_7."[14]

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Correspondence

(In the December issue we published a letter from Dr. Frank L. Tabrah, complaining of the rewards of pediatric practice. To this was appended a short statement by Dr. Lee Forrest Hill concerning the American Board of Pediatrics which was referred to in his letter. Under the Editor's Column we reprinted an editorial on pediatric rewards by Dr. A. H. Parmelee, Sr. Wishing to obtain the viewpoint of some of the younger pediatricians who are so vitally concerned, we asked Dr. W. G. Crook of Jackson, Tennessee, if he would comment on the discussion. Dr. Crook was selected because he graduated in 1942 and practices pediatrics in a small city without a large medical center. Dr. Crook's comments, in which his two associates, Dr. W. W. Harrison and Dr. S. E. Crawford, join, are so interesting that we publish it more in the form of a paper than the usual correspondence.—Ed.)

PEDIATRIC PRACTICE CAN BE REWARDING

W. G. Crook, M.D., W. W. Harrison, M.D., and S. E. Crawford, M.D.
Jackson, Tenn.

PEDIATRIC practice can be rewarding. As associates in a three-man group engaged in the general practice of pediatrics in Jackson, Tennessee (population 35,000), we find our practice extremely stimulating, satisfying, and rewarding. During the "pioneer" days of solo practice, one of us (W. G. C.) experienced a great many of the same frustrations detailed by Dr. Tabrah[1] in his recent letter to the Editor of the Journal of Pediatrics.

We are writing to discuss the letter of Dr. Tabrah as well as that of Dr. Hill,[2] and the editorial of Dr. Parmelee.[3] We wish to tell why, in our opinion, pediatric practice so frequently is frustrating to the well-trained pediatrician today. Finally, we will present our suggestions, detailing the steps which we think should be taken to better prepare the resident entering practice for the problems he will face.

Before discussing pediatrics and the pediatric practitioner, it is in order to review certain definitions and basic concepts. Putting it in very simple terms, pediatrics might be defined as that branch of medicine which deals with children. Why separate it from internal medicine? This separation is done for many reasons. Perhaps the most important of these is the fact that children *grow and develop.* The physician who treats children must have a fundamental knowledge of growth and development so he can recognize and adequately treat the diseases peculiar to childhood. Furthermore, he needs this fundamental knowledge to competently fulfill his responsibility in guiding and supervising the child's journey from birth to maturity.

What does the practice of pediatrics include? It includes a multitude of things. The care of premature and newborn infants, supervision of their feeding and immunizations, and the recognition and correction of any deviations from normal, are a part of the pediatrician's responsibility. He must be able to treat infectious diseases, metabolic diseases, collagen diseases, congenital diseases and malformations, and many others. The pediatrician must assume his responsibilities in preventive mental health measures, allergy prevention and treatment, and accident prevention.

The dramatic achievements in the field of pediatrics in the past fifty years are familiar to all of us. Davison,[4] several years ago, used the term "the pediatric shift" to describe the changing type of patient who is being seen in the children's hospitals and outpatient clinics of this country. More recently, Fischer[5] describes some of the challenges facing pediatricians today. These include accidents, adoption, school health, handicapped children, and juvenile delinquency. To this group, we think allergy also should be added.

In his letter and discussion of the progress of pediatrics, Dr. Tabrah[1] seemingly felt that pediatricians have worked themselves out of a job. Instead, as noted above, the pediatrician has even more challenging problems with which he must cope. The pediatrician of today, then, must be a new kind of specialist. Rather than learning "more and more about less and less," he must learn "more and more about more and more."

As is so beautifully presented in the book, *Health Supervision In Young Children,*[6] the pediatrician of today must recognize and assume his responsibilities for the care of the total child as a part of the family group. The pediatric specialist, whether he is engaged in teaching, research, or practice, must recognize and acknowledge the maxim that "anything of concern to the parent is of concern to the physician."

We are in agreement with Dr. Tabrah that the achievements of pediatrics eliminate the need for large numbers of pediatric internists to treat certain disease processes. However, pediatrics is infinitely more than the treatment of disease. It is a medical specialty demanding qualities, skills, and attributes of the highest type in order to achieve the goals of "constructive medicine."

We agree with Dr. Tabrah when he states that something is wrong with today's system of postgraduate training in that it "annually turns out scores of well-trained pediatricians who think their fascinating work in the teaching hospitals and clinics is a guarantee of an interesting and stimulating office practice." The need for a shift in emphasis in residency training was recognized and indicated recently by Dr. Arild Hansen[7] of the University of Texas. He stated, "It is the desire of every medical center interested in disorders of childhood to improve their residency training program. Although differences exist regarding the ultimate objectives at various centers, it is generally admitted that *the main purpose is to train specialized practitioners* of medicine for the childhood age group."

In this article, Hansen reported the results of questionnaires sent to all of the 220 members of the Texas Pediatric Society in regard to their own adequacy from past training and experience in the practice of pediatrics. About half of the group felt there should have been more emphasis in their training in allergy and psychiatric aspects of behavior problems. None of the group felt that "he should have had more training in such categories as Water and Electrolyte Disturbances, Metabolic Disorders, Contagious Diseases, Parasitology, Hematology, and typically Pediatric Diagnostic Problems."

The above report by Hansen answers very clearly certain of the problems posed by Dr. Tobrah.[1] It also explains why approximately one-third of the pediatricians in practice today are dissatisfied or unhappy with their practice.* It would seem, although the medical centers acknowledge that their main purpose is to train practitioners, that the "pediatric shift" with its new demands on the practitioners of pediatrics has created a considerable lag in so far as pediatric education is concerned.

In our opinion, the rapidly changing field of pediatrics is such that the medical centers have been too preoccupied with research work and with training residents for academic pediatrics. Do not misunderstand us, however. These aims of pediatric education are extremely important and very essential. At the same time, they should not be allowed to so overshadow the training of practitioners that the practitioner himself feels so ill equipped to handle the jobs thrust upon him that he quits in despair.

We very much disagree with Dr. Tabrah in his statements which indicate that the problems of pediatric practice are not important. We do not agree that there are "endless discussions with endless mothers of problems that are self-righting anyhow." In his paragraphs where he tries to analyze the question in regard to "What is wrong?" he asks whether it is the individual or the specialty. We suspect, as he says, that in his case it is both. We agree with him and with Dr. Parmelee[3] that the pediatrician must have certain inherent characteristics of personality in order to enjoy pediatric practice. As outlined by Dr. Parmelee, these include "gentleness, friendliness, thoughtfulness, trustfulness, respectfulness, and a sense of humor." The pediatrician, perhaps foremost of all, must like people. He must have something of the missionary or evangelistic spirit in order to work on and deal with many of the discouraging problems of parent-child relationships which, at times, seem almost insoluble. Again quoting Dr. Parmelee,[3] he must have "the poise of a sound philosophy permeated by optimism."

We feel that part of Dr. Tabrah's disillusionment and frustration is due to the fact that either because of inherent personal factors or to the circumstances of his training, he somehow arrived at a point of view which leads him to feel that most office practice is concerned with "trivia" and might well be handled by a person other than physicians. Every pediatrician in practice who is to be satisfied must have something of the feeling expressed by Solnit and Senn[8] who stated, "Every patient is an interesting person. It can be as satisfying and important to care for a six weeks old infant who is well or a child who is going to camp as one who suffers from a rare disease." Washburn[9] expressed a somewhat similar thought stating, "The diagnosis of a disease becomes no longer an end in itself but rather a means toward the real goal of helping this particular child to get well and to remain in happy and healthy adjustment in the future."

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*This figure was obtained in a survey conducted by Medical Economics, Inc., Oradell, N. J., and published in the November, 1956, issue.

In attempting to analyze further Dr. Tabrah's frustrations and disillusionment, as well as that of many other unhappy pediatric practitioners with whom we have discussed this subject, there are other pertinent observations. It is well known that we all achieve satisfaction from doing a job well. We derive pride and gratification in using our talents and skills either inherent acquired. We dislike things about which we know little. These are normal reactions of the human personality. Applying these maxims or premises to the situations faced by the pediatric resident entering practice, it is not difficult to see why as many as one-third of those trained in the customary manner are unhappy in practice. As is pointed out by Dr. Tabrah,[1] too often the practicing pediatrician is unable to use the bulk of his training unless he is associated with a teaching hospital or in some consultant position. On top of this, he is faced with a multitude of problems presented by a multitude of mothers, both in person and on the telephone, that he is not equipped to solve or handle to his or to the mothers' satisfaction.

In our opinion, the reasons why a practicing pediatrician may be frustrated and unhappy are rather easy to see. The more difficult problem lies in regard to what can and should be done to remedy this situation in the residents entering practice in the years to come. The regional conferences sponsored by the Committee on Medical Education of The American Academy of Pediatrics have been discussing and exchanging ideas to help in the solution of this problem during the past five or six years. Progress has been and is being made. Even so, it is our feeling that more definitive steps are in order.

SUGGESTED SOLUTIONS TO THE PROBLEM

The nature of the problems involved in training a physician for pediatric practice are such that simple answers are not to be found. We agree with Dr. Powers[10] that "the emphasis (of a pediatric training program) is not on content so much as on quality." Dr. Powers further stresses the importance of "organized, focused experience under inspiring guidance in several aspects of one discipline, high standards, sharp critiques and the ability to accurately and intelligently appraise, relate, and apply data in the humane practice of medicine. . . ." "Physicians so trained and conditioned are prepared to meet the exigencies of future responsibilities in much wider fields of medicine."

We would not, for one instant, wish to sacrifice the type of training of which Dr. Powers speaks. We would not desire to "dilute" the training given to us during our internship and residency years. Nothing should be taken away. More should be added. The question is how. Here are the suggestions of practicing pediatricians.

1. *Promote practice in pediatric groups.* We would discourage any resident from going into the solo practice of pediatrics. This is especially true if the city or community does not have a teaching hospital with available interns and residents. For the individual in solo practice, the disappointments and frustrations will far outweigh the rewards and achievements. He may do much pioneer work but it will be long and hard and frequently unrewarding. The solo pediatrician has no kindred spirit with whom he can share the thrill of a sharp diagnosis. He has no "built-in consultant" to lean on when the diagnosis seems obscure. He has no one to hold him up and "cover" for him when he needs a day or a week off for a vacation or a medical meeting. Unless he has income other than that of his practice or unless he starts out with a sizable nest egg, he is unable to equip his office with the tools so essential for modern pediatric practice. These tools include a first-class laboratory staffed by trained personnel. He has become accustomed to the facilities of an x-ray machine in his hospital training. By himself, it is difficult to afford one. The expense of office equipment of various kinds may be too great for his budget.

The solo practitioner soon becomes so bogged down with the responsibilities of routine office practice that even when the severely ill child or the one with a diagnostic problem comes in, he has insufficient time to spend with the child and so may end up referring him back to the medical center for treatment or diagnosis. (This happened frequently to one of us [W. G. C.] during his year of solo practice.)

2. *We would show more concern for medical economics.* The conscientious pediatrician knows that one does not enter pediatrics for its financial rewards. Nevertheless, this does not mean that the practicing pediatrician can ignore the economic or business side of medical practice. It is completely illogical for medical and pediatric educators to absolutely ignore this aspect of training an individual for practice. If the business side of a pediatrician's practice is not carefully planned and laid out, an adequate return may not be forthcoming. Without an adequate return, he cannot employ well-trained personnel. He cannot purchase needed equipment. In short, he cannot distribute to his medical consumers the type of medical skills and services of which he is capable.

Admittedly, everything cannot be crammed into a two- or three-year residency period of training. Our suggestions for achieving such training would be essentially as follows. Each resident, after the completion of his hospital training and before going into practice, should spend three, six, or twelve months' time in a preceptorship type of arrangement with an established pediatric group. His remuneration during this preceptorship period should be liberal enough to make it attractive to him. During this period he could learn much that he needs to know in regard to the setup of an office, office forms and records, equipment, billing, etc. Needless to say, the groups receiving the graduating residents should be as carefully selected as is a hospital for residency training.

Management counseling should be made use of in order to achieve the best in modern techniques in office planning and setup.

An interest in the economic side of pediatric practice should stimulate leaders in the field of pediatrics to take a more active interest in obtaining adequate insurance coverage of illnesses peculiar to infants and children.

3. *Exchange of Personnel.* Academic pediatricians who are to have a part in training pediatricians for practice should spend some time in the general office practice of pediatrics. Just as the football coach who has played the game himself tends to make a better coach, the individual who has the responsibility for teaching will be far better qualified if he is familiar with the problems his students will be called upon to face.

A suggested method of achieving greater familiarity with practice situations would be by the exchange of academic pediatricians with practicing pediatricians. In such exchange situations, the practicing pediatrician could be utilized for lectures, demonstrations, or discussions during his stay at the medical center. At the same time, his practice would be covered and the medical center pediatrician could be learning the problems of the practice. This would solve certain of the problems of diluting the residency or internship by bringing the practicing physician into the medical center. Too often, the pressures of time weigh so heavily on the attending part-time man who so generously helps in the outpatient department or on the wards in the medical teaching load, that he cannot devote the time which he might otherwise like to spend.

4. *Improved techniques of communication.* Admittedly, as noted by Dr. Powers[10] in describing Dr. William Stewart Halsted, Professor of Surgery at the Johns Hopkins University, there are some "men who teach best by not teaching at all." Admittedly, some few "greats" of medicine may be wonderful teachers even though, like Halsted, they are unable to verbalize well in a lecture. "His comments could not be heard on the front row of the clinic and he did not use lantern slides skillfully." At the same time, all teaching personnel could benefit from expert advice and consultation from individuals trained in the science of communication. Dr. Samuel Johnson once said, "People have got a strange opinion that everything should be taught by lectures." Charts properly prepared, filmstrips, slides, movies, and other visual aids should have maximum utilization in our medical teaching at all levels.

Books, pamphlets, and other teaching aids which help the practicing pediatrician interpret to the parents the things which they want to or need to know also should receive increased emphasis.

CONCLUSIONS

Pediatric practice can be rewarding. That is not to say that it automatically will be rewarding to the resident entering practice today. However, as Dr. Hill[2] pointed out, there is a great general interest in pediatrics among graduating medical students at the present time. Many young men seem to be possessed of the "inherent individual qualities" spoken of by Dr. Parmelee[3] which go to make a good pediatrician. At the same time, having experienced many of the frustrations and disappointments of which Dr. Tabrah speaks, we feel that there is a definite need for a change in the goals and in the perspective of pediatric education.

We cannot agree with Dr. Tabrah's conclusions that pediatricians, to be happy, "must find their place in large centers, mainly as consultants." However, we very much agree with him when he states that the pediatrician, to be happy, must find a place "where his knowledge is essential and his talents are fully utilized."

The needs, the challenges, and the demands for skilled and highly trained pediatricians are greater today than ever before in every part of our country. Pediatric education can and must more adequately prepare the pediatrician of today and tomorrow.

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The American Board of Pediatrics has announced its schedule for oral examinations to be held in 1958. These are as follows:

Memphis, Tenn., March 21, 22, and 23, 1958.

Atlantic City, N. J., May, 3, 4, and 5, 1958.

Cincinnati, Ohio, June 13, 14, and 15, 1958.

Chicago, Ill., Oct. 24, 25, and 26, 1958.

New York, N. Y., Dec. 5, 6, and 7, 1958.

The following rules will govern selection of candidates:

1. Candidates must have passed a written examination.
2. Candidates will be called in the order in which their applications were received. Since only a predetermined number can be examined orally in a given year, those enrolled for the written examination who are in excess of that number will be designated as "alternates." They may be called to fill vacancies that develop or may not be called until 1959.
3. Candidates will not be called far in advance of their eligibility date. Therefore, please do not choose a date more than one month prior to the same.
4. Candidates should make a second choice as the list for each session must be filled. "Alternates" should also list a first and second choice and, so far as possible, these will be heeded. (Refusal of an appointment will not prejudice subsequent call but candidates are expected to accept an appointment within two years following passing of the written examination unless an extension is granted by the Board, upon written request by the candidate.)
5. All candidates for oral examination in 1958 should make their choices *now*. Do not wait to learn the result of your written examination. So far as possible, your choices will be heeded.

Dr. Victor C. Vaughan III has been appointed chairman, department of pediatrics, Medical College of Georgia, Augusta. Dr. Vaughan has served as assistant professor, Yale University School of Medicine, and recently as associate professor of pediatrics, Temple University School of Medicine, Philadelphia.

At the annual meeting of the **American Academy of Pediatrics** held in Chicago, Oct. 9, 1957, Dr. Stewart Clifford of Boston took over the presidency for 1957-1958, and Dr. James Overall of Nashville, Tenn., was elected President-Elect for 1958-1959.

The Department of Pediatrics of the University of Colorado School of Medicine announces a *Postgraduate Course in Pediatrics* Sept. 4-9, 1958, to be held at Estes Park, Colo. The first part, September 4-6, will be devoted to Clinical and Research Advances in Pediatrics. The second part, September 8-9, will be devoted to Child Guidance Problems under the leadership of Dr. Sherman Little. The course will be held at the Stanley Hotel in Estes Park, providing a pleasant and relaxed environment with ample recreational and resort resources for the hours when meetings are not held. No formal meetings will be scheduled for Saturday afternoon or Sunday so that this time may be used for rest, fishing, swimming, riding, golfing, hiking, and mountaineering. Wives and children are welcome and special entertainment will be provided for them. Information as to fees, hotel reservations, etc., may be obtained from the Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Ave., Denver 20, Colo.

The twenty-sixth annual series of the **Benjamin Knox Rachford Lectureships** will take place in Cincinnati, Ohio, on Tuesday and Wednesday evenings, Feb. 11 and 12, 1958, at 8:30 P.M. Dr. Robert A. Good, American Legion Memorial Heart Research Professor of Pediatrics at the University of Minnesota, will deliver these lectures in the auditorium of the Children's Hospital Clinic and Research Building. On February 11 Dr. Good will lecture on "Disturbances in Agammaglobulinemia and Antibody Synthesis," and on February 12 the subject will be "Diffuse Renal Diseases in Childhood."

A refresher course in pediatrics will be conducted at St. Christopher's Hospital for Children, Philadelphia, by the Pediatric Department of **Temple University School of Medicine** on May 21 to 24, 1958. Each half day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 North Lawrence St., Philadelphia 33, Pa.

A major residency fellowship program, designed to encourage more young physicians to specialize in pediatrics, has been established by Wyeth Laboratories.

Under the program, 20 fellowships will be awarded annually to interns or those who have recently completed their internship. Each grant will cover the required two-year pediatric training program and will carry an annual stipend of $2,400. The cost of the first three years of the program will be $195,000.

The names of the first group of recipients will be announced in the spring of 1958, and the fellowships will be effective the following July 1. Participation is limited to citizens of the United States and Canada.

The fellowship recipients will be selected by a committee composed of eminent pediatricians, representing both the clinical and educational aspects of that specialty. The names of the members will be announced later.

The grants will be awarded to young physicians evidencing a strong interest in pediatrics, and demonstrating good character, conscientious and able performance of duties, academic competence, and financial need. Those receiving grants may attend the hospitals of their own choosing, as long as the residency training program is properly accredited.

The **First Asian Regional Paediatric Congress** will be held in Singapore from May 26 to 30, 1958. The regions invited are the Indian Sub-Continent, the Far East, South-East Asia, and Australasia. Any doctor who is interested in attending should write to the Organising Secretary, The First Asian Regional Paediatric Congress, the Paediatric Unit, General Hospital, Singapore 3.

The **Seventh Congress of the International Society of Hematology** will be held in Rome at the Palazzo dei Congressi, EUR, on Sept. 7 to 13, 1958.

The official languages of the Congress will be English, French, German, Italian, and Spanish.

Preliminary program: (1) immunohematology; (2) hemorrhagic disorders; (3) leukemia; (4) anemia; (5) nucleonics; (6) the spleen and the reticulo-endothelial system.

For further information please write to: Segreteria del VII Congresso Internazionale di Ematologia, Istituto di Patologia Medica, Policlinico Umberto I, Roma (Italia).

The Congress of the International Society of Blood Transfusions will be held at the same Palazzo dei Congressi on September 3 to 6.

Books

Fundamentals of Clinical Fluoroscopy, ed. 2. Charles B. Storch, M.D., New York, 1957, Grune & Stratton. 340 pages. Price $8.75.

This book is intended to present the fundamentals of fluoroscopy for interns and residents, for physicians in general practice, and for specialists who are interested in fluoroscopy as a diagnostic aid in the practice of medicine.

Production of the fluoroscopic image and the physiology involved in adaptation and seeing the fluoroscopic image are briefly but clearly explained. The effect of x-ray beam projection in regard to positioning the patient is not as detailed as might be desired, but the method of demonstrating that portion of the lung posterior to the diaphragm is especially well illustrated.

There is also limited discussion of x-ray interpretation utilizing the fluoroscopic approach in diagnosis of some disease entities; e.g., more emphasis is placed on fluoroscopy in x-ray interpretation of the small bowel than is warranted relative to the space devoted to other sections.

Some of the dangerous biological effects of x-ray, particularly on skin and blood, are mentioned in the first chapter, and the rules for the proper use of the x-ray equipment and protective devices are listed and explained and should be closely followed for the protection of the fluoroscopist. It is unfortunate, however, that the author did not emphasize the need for eliminating unnecessary fluoroscopic examinations such as routine chest fluoroscopy and fluoroscopic examination for fractures.

The pediatrician who uses fluoroscopy largely for chest examinations will be provided with valuable basic information regarding a proper examination routine. Normal shadows which may cause confusion when projected over the lung are explained along with those that occur with pathology. Physiological variations in the chest are also noted.

In general, this is a practical, clearly written, well-illustrated book that has been made concise enough for quick reading yet complete enough to provide a primer on fluoroscopy of value to all physicians wishing to utilize x-rays for diagnostic purposes.

M. H. N.

The Salient Points and the Value of Venous Angiocardiography in the Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart. Benjamin M. Gasul, M.D., Gershon Hait, M.D., Robert F. Dillon, M.D., and Egbert H. Fell, M.D., Springfield, Ill., 1957, Charles C Thomas, 80 pages. Price $3.50.

This book, in contrast to its lengthy title, is very clear and presents concrete information of value to the clinician interested in congenital heart disease. Proper emphasis is given to the need for evaluation of a patient prior to angiocardiography for successful interpretation of the findings. The author classifies the cyanotic malformations into those which can be recognized by this study and those in which angiocardiography may be of help but cannot make a definitive diagnosis.

Some of the cases are proved by autopsy, some by cardiac catheterization, others by surgery. There are certain illustrations of cases in which the reader cannot help but wonder by what method the diagnosis was proved. A notation about this in each case would have given the book added value.

The book is highly recommended for its simplicity in presentation and fine quality of angiocardiographic films.

D. G. M.

Diseases of the External Ear. Ben H. Senturia, M.D., Springfield, Ill., 1957, Charles C Thomas, 211 pages. Price $8.50.

This monograph by the Associate Professor of Otolaryngology of the Washington University School of Medicine is based in large part on a 5-year study and research supported by contract grants made by the United States Air Force. Infections of the external ear are very common in some parts of the country, particularly the southern coastal areas, and have been a problem in some military establishments. The text begins by discussing the factors, such as contamination, and heat and humidity, that have been considered responsible for the disease. This is followed by chapters on the anatomy and pathology of the external ear, which are beautifully illustrated with drawings and original photomicrographs. Another chapter presents the experimental laboratory studies in which it was found that contamination with Pseudomonas combined with trauma was essential in the production of the disease. The final chapters take up prophylaxis and treatment. A well-selected bibliography follows each chapter. This is an excellent contribution to our knowledge of a troublesome disease, and the volume is an important addition to medical literature.

Handbook of Orthopaedic Surgery, ed. 5. Alfred Rives Shands, Jr., M.D., St. Louis, 1957, The C. V. Mosby Co., 630 pages. Price $9.75.

This book presents a completely condensed and well-organized publication of the subjects of orthopedic surgery. The quality of the bibliography qualifies this handbook for students of medicine and practicing physicians in the specialty, as well as investigators. The author's style using the elements of simplicity in statements of concepts, clarity of principle, and excellence of illustration, make this edition an outstanding publication.

P. R. H.

Editor's Column

JOURNAL OF PEDIATRICS VISITING LECTURESHIPS

THE Editorial Board of THE JOURNAL OF PEDIATRICS, responsible for administering The Journal of Pediatrics Educational Fund as announced in the last issue, is establishing a number of Visiting Lectureships for pediatric clinics. The Lectureship at an individual clinic will be of one week's duration. The Lecturer will be appointed to visit a single clinic, or, especially in the case of foreign pediatricians, may be scheduled to visit up to four clinics. He will receive from the fund an honorarium and expenses.

The motivating thought of the Lectureships is that much could be gained by having a Lecturer who, during his week's visit, would spend his time mingling with the staff in an informal way and taking an impromptu part in the work of the clinic—ward rounds, teaching, conferences, and laboratory services. The Editorial Board proposes to invite both foreign and American pediatricians, or scientists working in a field related to pediatrics, as Lecturers. This program has been discussed with a number of departmental chiefs of service who have without exception approved the project.

A special committee of the Board has been appointed to select the Lecturers and clinics for 1958. Every effort will be made to meet the needs or desires of the individual clinic. So far as possible a different group of clinics will be used each year. Details as to the Lecturers and clinics selected for 1958 will be announced later.

EDITORIAL BOARD CHANGES

SOME time ago Dr. Veeder, Editor of the JOURNAL since it was started in 1932, asked the Editorial Board to select a new Editor as he wished to retire. At a recent meeting of the Board, Dr. Waldo E. Nelson was appointed to succeed Dr. Veeder and will take over the Editorship at the end of the current year. There will be no change in the general policies of the JOURNAL.

At the same meeting, Dr. Robert E. Cooke, professor of pediatrics at the Johns Hopkins, Baltimore, was elected to membership on the Board.

The Editorial Board of THE JOURNAL OF PEDIATRICS is an independent, self-perpetuating body which has complete control of the JOURNAL and determines its policies.

CASE HISTORIES AND METHODS

The mother and father of the children in this study were unrelated Negroes who had always resided in South Texas. They were both 38 years old and in good general health. Neither has had any known thyroid enlargement. The mother enjoyed excellent health throughout all of her pregnancies, requiring no medications other than routine vitamins and iron. The diet of the family was typical for the area and contained no known goitrogens. Seven uncomplicated pregnancies had resulted in seven full-term infants. Four of these children were goitrous and two were not. One child died accidentally at the age of 2 months.

The children's maternal great-aunt had a large asymptomatic goiter for many years prior to her death at 70 years of age. A maternal uncle had a goiter removed at the age of 26 because it was causing "choking spells." The goitrous siblings were as follows:

B. M. T., a 15½-year-old girl in whom a goiter was first noted at 14 years of age, had always been euthyroid and had had normal menses since the age of 11. The goiter had gradually increased in size. When first seen by us, she was a normal adolescent with a diffuse moderately enlarged, soft, symmetrical, nonnodular thyroid.

D. T. and J. T. were 11½- and 7½-year-old girls, respectively, in whom small goiters appeared at an unknown age. They were euthyroid children with small, soft, symmetrical, nonnodular goiters.

L. T., a 28-month-old boy with a birth weight of 6 pounds 8 ounces, was noted to have a goiter at birth. His pulse, blood pressure, activity, and weight gain in the neonatal period were completely normal. There was no exophthalmus. Subsequent periodic observations revealed no physical abnormalities other than persistent yet variable size of the goiter and frequent mild to severe upper respiratory infections. On repeated occasions the goiter was noted to be largest during the acute infections, with diminished size during periods of good health.

This child had shown no deviation from a normal growth and developmental pattern. The general well-being including activity, appetite, bowel habits, and disposition had remained completely normal. Other than the goiter, chronic nasal obstruction, and hypertrophied tonsils, the physical examination was normal in all respects.

At the time studied, this normal-appearing 28-month-old Negro boy had a normal height age with normal proportions. He was active and had average intelligence. There were twenty well-formed noncarious teeth. The skin was smooth, warm, and soft. There was a diffuse enlargement of the thyroid which was about six times normal size. The left lobe was slightly larger than the right, but the entire gland was smooth, soft, and nonnodular. There was no thrill or bruit. Repeated determinations of the bone age, serum cholesterol concentrations, and alkaline phosphatase levels have been normal. Studies of stable and radioiodine metabolism will be given in detail.

J. T. and C. T., 9- and 4½ year-old-boys, were the nongoitrous siblings in this family.

Determinations of the protein-bound iodine and butanol-extractable iodine were performed at various intervals on patients L. T. and B. M. T.*[1] The thyroidal uptake of I^{131} was determined on some of the goitrous siblings.

The effect of potassium thiocyanate on the retention of accumulated iodine by the thyroid was studied by administering tracer amounts of I^{131}

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*Determinations were performed by Bio Science Laboratories, Los Angeles, Calif.

3 to 4 hours prior to the oral administration of potassium thiocyanate in doses of 0.75 to 2 Gm. The uptake of I^{131} was calculated immediately before giving thiocyanate, and external counting was done at frequent intervals up to 90 minutes after the dose was given.

In two members of the family (L. T. and B. M. T.) chromatography of the plasma was done after administration of I^{131} according to the method of Stanbury.[6] Acid butanol extracts, to which carrier amounts of diiodotyrosine, thyroxine, and triiodothyronine had been added, were applied to Whatman No. 1 filter paper strips and developed for 24 hours by use of a dioxane-butanol-ammonia system. After the carrier had been located on the paper by spraying with diazotized sulfanilic acid, the paper was cut into 1 cm. strips and these were counted in a well-type scintillation counter.

Samples of plasma obtained from B. M. T. at various intervals after administration of I^{131} were first extracted with acid butanol, then washed three times with 4 N sodium hydroxide containing 5 per cent sodium carbonate in a manner similar to the method for determining butanol-extractable iodine.[19] Carrier diiodotyrosine and thyroxine were added prior to the alkaline wash. The radioactivity of the alkaline-soluble and butanol-soluble fractions was compared to the total activity prior to fractionation. The butanol-soluble fraction was neutralized with 40 per cent sulfuric acid and chromatographed in the butanol-dioxane-ammonia system. The carrier thyroxine was located [illegible] into 5 cm. strips [illegible] in a well-type [illegible]

RESULTS

I^{131} Uptake St[illegible] studies were done [illegible] ginning at 26 days [illegible] can be seen that [illegible] sive increase in the [illegible] iodine until 2 3/12 [illegible] was a decrease and [illegible] the 6-hour as compared [illegible] hour uptake. It may [illegible] although at 2 3/12 years [illegible] decrease in the 24-hour [illegible] ever determined, [illegible] avidity of the thyro[illegible]

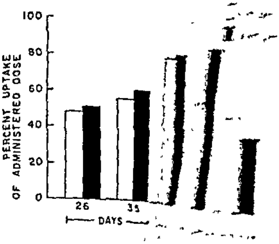

Fig. 1.—Six- and [illegible] of I^{131} by the thyroi[illegible] L. T., who had a [illegible]

On two occasi[illegible] were done on [illegible] initial uptake [illegible] hours and 75 [illegible] the second, [illegible] was 62 per [illegible] and 24 hours [illegible]

PBI and B[illegible] of the prot[illegible] tanol-extract[illegible] tient L. T. [illegible] protein-bo[illegible] were at [illegible] limit of normal (8 μg per cent) except in the last instance when the value was 8.5 μg per cent. It may be seen that on the two occasions when butanol-extractable iodine determinations were done, the resultant values were well within the range of normal (3.5 to 6.5 μg per cent). It was originally felt that the elevated values of the PBI in the first weeks of life were in accordance with the normal findings of others.[20]

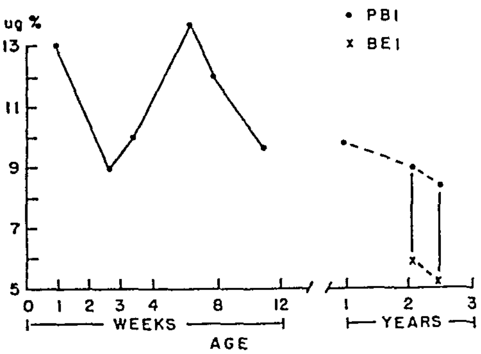

Fig. 2.—Chemical protein-bound iodine (PBI) and butanol-extractable iodine (BEI) determinations on patient L. T. from 1 week to 2½ years of age.

Determinations of the protein-bound iodine were obtained on patient B. M. T. on three occasions. The values were 5.1, 5.7, and 7.6 μg per cent, respectively. At the time that the latter value was obtained, the butanol-extractable iodine was 4.8 μg per cent.

Although few determinations of butanol-extractable iodine were made simultaneously with total protein-bound iodine in these two patients, an average disparity of 3.2 μg was observed. This value is above the maximal difference in normal individuals.[19, 21]

Thiocyanate Studies.—Thiocyanate studies were performed on 5 members of this family group; the 4 siblings with goiters all demonstrated a release of thyroidal I^{131} when oral potassium thiocyanate was administered. Patient L. T. (Fig. 3) had 60 per cent thyroidal retention of a tracer dose of radioiodine after 3 hours. Following 1.0 Gm. of oral KSCN the accumulated thyroidal I^{131} decreased to 20 per cent in the subsequent 75 minutes. B. M. T. (Fig. 4) accumulated 93 per

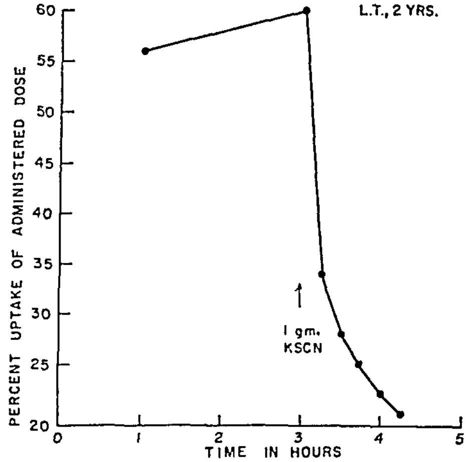

Fig. 3.—The effect of 1 Gm. of orally administered KSCN on the thyroid retention of a tracer dose (1 μc) of accumulated I^{131} in patient L. T. at the age of 2 years.

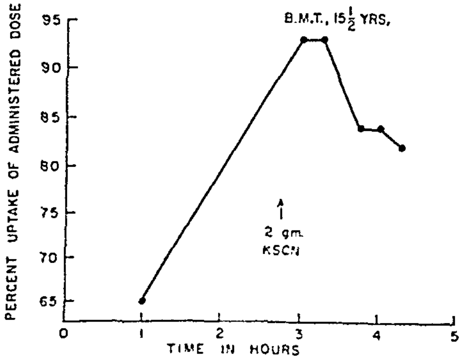

Fig. 4.—The effect of 2 Gm. of orally administered KSCN on the thyroid retention of a tracer dose of accumulated I^{131} in the oldest goitrous sibling, B. M. T., at the age of 15½ years.

cent of the administered radioiodine in 3 hours and showed a decrease of 11 per cent of the radioiodine retention 90 minutes following 2 Gm. of KSCN. The other two siblings with small goiters (Fig. 5) showed slight but definite discharge of thyroidal I^{131} following a 1 Gm. dose of thiocyanate. C. T., the nongoitrous sibling (Fig. 6), failed to show the phenomenon of thyroidal I^{131} release following administration of KSCN.

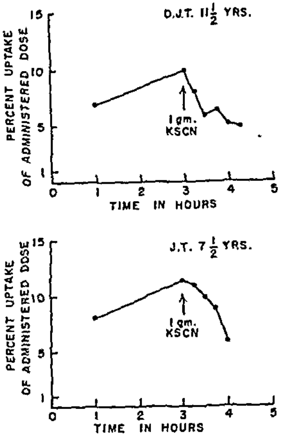

Fig. 5.—The effect of 1 Gm. of KSCN on the accumulated I^{131} in the thyroids of the 2 siblings with small goiters.

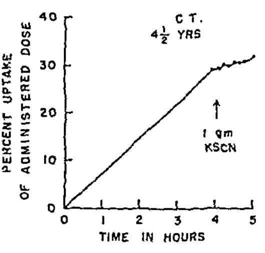

Fig. 6.—The effect of thiocyanate administration on the accumulated I^{131} in the thyroid of a nongoitrous sibling, C. T., aged 4½ years.

Chromatographic Studies and Protein-Bound I^{131} Fractionation.—At 28 months of age, patient L. T. was given 50 μc of I^{131}, and 5 ml. samples of plasma were obtained at 4, 8, 12, 24, and 30 hours. These samples were chromatographed on paper in the butanol-dioxane-ammonia system. At 4 hours, radioactivity was detected in the carrier thyroxine spot and appeared to be present in increasing amounts in the remainder of the chromatographs. Radioactivity in the carrier triiodothyronine spots was not found with certainty at 8 hours but was found in the 12- and 24-hour chromatograms.

Although there was proportionately more radioactivity in the thyroxine spots than in the triiodothyronine spots, their specific activity was not estimated. In none of the chromatographs was significant radioactivity found in the carrier diiodotyrosine or monoiodotyrosine spots.

Patient B. M. T. was given 200 μc I^{131}, and samples of plasma were obtained at 4, 18, and 24 hours. Duplicate chromatographs were run on 2 ml. aliquots of plasma in the butanol-dioxane-ammonia system. The results of these chromatographs were in accordance with those of patient L. T. An 18-hour chromatograph of the acid butanol extract of the plasma from B. M. T. is demonstrated in Fig. 7.

Before these samples were chromatographed, the amount of radioactivity in the dried residue of the acid butanol extracts was determined. Activity of the residues after alkaline partition are shown in Fig. 8. Development and counting of the chromatograms of the butanol-soluble fraction revealed significant radioactivity only in the thyroxine and triiodothyronine areas.

Histopathology.—Biopsies of the thyroid glands of patients B. M. T. and L. T. were attempted by use of a Silverman needle. The procedure was successful only in patient L. T. Fig. 10 reveals that the tissue was made of compactly arranged irregular-sized follicles of essentially two types. Some of the follicles were lined by cuboidal epithelium and the lumina of these follicles were free of colloid. Other follicles were lined by low, flattened cuboidal epithelium and contained dark-staining material in the lumina, giving the appearance of inspissated colloid. The interfollicular tissue was made up of poorly cellular collagen.

Results of Therapy With Desiccated Thyroid.—Patient L. T. was started on desiccated thyroid in doses of 60 mg.

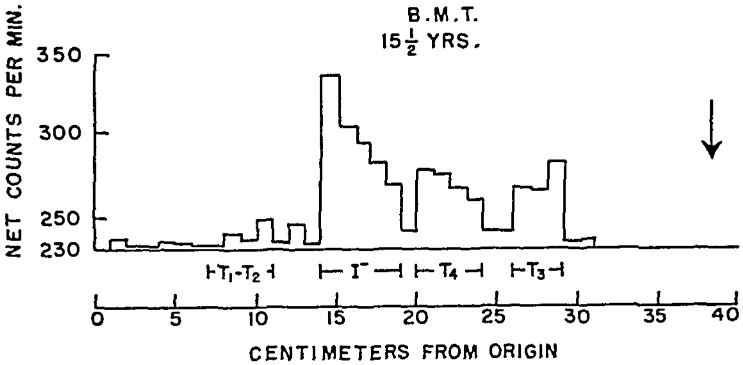

Fig. 7.—The labeled components of 2 ml. of serum from B. M. T. 18 hours after administration of 200 μc I^{131}. The ordinate is in net counts per centimeter of paper strip. The abscissa is in centimeters from the origin of the chromatogram. The solvent front is indicated by the arrow. T_1 = mono-iodotyrosine; T_2 = di-iodotyrosine; T_3 = tri-iodothyronine; T_4 = thyroxine; I = Iodide.

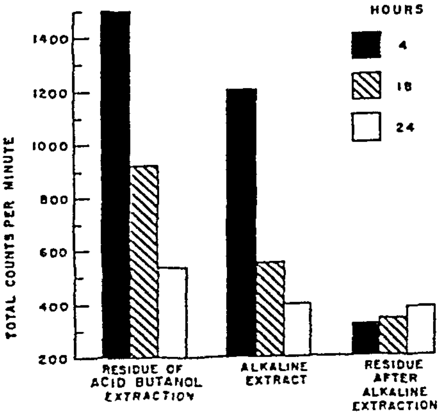

Fig. 8.—Radioactivity of the acid butanol extracts before chromatography and the alkaline-soluble and butanol-soluble fractions obtained serially from B. M. T. after the administration of 200 μc of I^{131}. The ordinate is in total counts per minute per residue prior to chromatography. The method of alkaline partition of the butanol extracts is described in the text.

daily; after two months of this therapy there was a marked reduction in thyroid size. Patient B. M. T., although receiving 120 mg. of desiccated thyroid, has been on therapy too short a period to evaluate a change in thyroid size. The other siblings with goiters were not treated. Repeated observations and laboratory data failed to reveal any evidence of hypothyroidism in these children.

The younger sibling, L. T., had a congenital goiter and a marked release of accumulated radioiodine following thiocyanate administration (Fig. 3), and it is possible that in later life thyroxine synthesis might be inadequate to maintain his euthyroid state. On the other hand, B. M. T., who developed a large goiter at the age of 14, had a similar defect in synthesis, but had established a normal menarche when first studied at 15½ years of age.

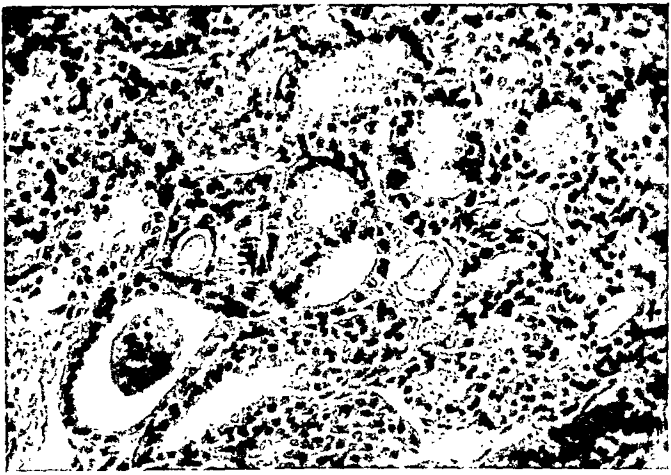

Fig. 9.—Section of thyroid obtained from patient L. T. by needle biopsy. (Hematoxylin and eosin stain.)

DISCUSSION

The foregoing data show that the four goitrous siblings of this family have a familial defect in the ability of the thyroid to organically bind iodine. However, unlike the goitrous cretins previously described with this same defect, the thyroids of these children were able to synthesize adequate amounts of thyroxine under increased stimulation with thyrotropin and subsequent goiter formation. Re-

The other siblings, D. T. and J. T., who had small goiters, demonstrated only slight but definite release of accumulated radioiodine after thiocyanate administration (Fig. 5).

Apparently not all of the siblings manifested this inborn error of metabolism, since C. T., a nongoitrous male sibling, showed no release of I^{131} when thiocyanate was administered.

An interesting observation in patient L. T. was the variation in thyroid size which occurred from time to time. During infections his thyroid would increase in size, suggesting either an increased need for thyroid hormone or further interference with thyroid function as a result of the infectious process. The other goitrous siblings did not demonstrate this variation in thyroid size.

It should be pointed out that the two siblings with large goiters had abnormally high accumulations of thyroidal radioiodine 3 hours after administration of I^{131} (60 and 93 per cent), whereas the two siblings with small goiters had normal 3-hour uptakes of I^{131} during the thiocyanate studies.

Further proof of adequate thyroxine synthesis was the normal values for the butanol-extractable iodine found in patients L. T. and B. M. T. In L. T. the protein-bound iodine was constantly elevated above normal. In both patients there was a disparity between the PBI and BEI when they were measured simultaneously. These findings have been reported as occurring in patients with struma lymphomatosa[21, 22] and in a patient with goiter and myxedema following prolonged iodine administration.[23] The studies presented here failed to clarify further the nature of this iodinated protein complex which contributes to the fraction not extractable with butanol.

It should be pointed out that this discrepancy in PBI-BEI has not been demonstrated in goitrous cretins with this same defect because the protein-bound iodine concentrations have been extremely low in those in whom it has been determined.[1, 2, 7]

It is felt that the chromatographic studies as well as the fractionation procedures clearly demonstrated the presence of labeled thyroxine in the plasma of the two patients studied. Quantitatively it is impossible to say whether the amounts found were normal; however, in view of the normal butanol-extractable iodine levels, it might be assumed that the levels of thyroxine were normal. Although not demonstrated with certainty, there was a suggestion of a delay in the appearance of labeled thyroxine in both patients. There was a suggestion of increased counts in the diiodotyrosine spot in one of the chromatograms (Fig. 7), but this was not found in the other chromatograms and was considered to be an artifact.

The histologic appearance of the thyroid of patient L. T. suggested that some of the follicles were hyperfunctioning and some were nonfunctional. The histopathology differed from that found in goitrous cretins with identical defects in organic binding of iodine in that there were no areas of adenoma, colloid cysts, fibrosis, or necrosis.[1, 2, 7] One may speculate that these goitrous cretins were under more intense stimulation with thyrotropin and the duration of stimulation had been a factor in the production of these findings. It is of interest that when the biopsy material from patient L. T. was compared with that from a euthyroid child with a large goiter having a different defect in synthesis, the histopathology of the two was identical.

SUMMARY

A family of six Negro children, four of whom had goiters, has been described. The goitrous children were found to have a defect in organic binding of iodine, as shown by the release of thyroidal radioiodine after the administration of potassium thiocyanate. Of great interest was the fact that these children have remained euthyroid as determined by clinical and laboratory observations. Studies of thyroid metabolism have been presented and the histopathology of a thyroid biopsy from one of the children has been described.

It was concluded that this family of goitrous children clearly demonstrated examples of "simple" nontoxic goiter due to an intrinsic metabolic defect in thyroxine synthesis.

We wish to express our thanks to Dr. C. T. Teng and Mr. W. D. West for their aid in carrying out the I^{131} studies and to Miss Dolores Rubin for invaluable technical assistance.

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Infant Mortality Statistics

"It will be perceived that these 'stillborn and premature birth' interments number equal to *one-fifth* of the entire infant mortality of the last half century, and hence ought not to be overlooked in any estimate made upon this subject. Apart, however, from their numbers, they must be included for another and a weightier reason, since the causes of mortality among children of tender age are, in a multitude of cases, to be found only by extending our inquiries to their *intra-uterine* life, and the physiological state of the parents, but especially the sanitary condition of the mothers, their hygienic and moral habits and circumstances. Nothing can be more certain than that the viability of the infant after birth, and its tenacity of life, depend very greatly upon the condition, circumstances, habits, and health, of the parents, particularly those of the mothers, during every period of pregnancy; and hence, pathological and demoralizing agencies, operating upon parents in reproduction, and during utero-gestation, are often the sources of 'premature birth and stillborn' cases, but not less the cause of early death in their offspring after birth, and resulting in a vast proportion of the infant mortality so sadly and so universally deplored. These considerations may suffice to justify our plea for including the stillborn interments among the victims of infant mortality."

FROM A REVIEW OF DR. D. M. REESE'S ARTICLE IN THE TRANSACTIONS OF THE A. M. A., Vol. X. 8vo., pp. 676, Philadelphia, 1857.

A STUDY OF PATHOLOGY OF STILLBIRTHS AND NEONATAL DEATHS IN SOUTH INDIA

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THIS paper represents a study of the pathology of stillbirths and the newborn infant as seen in the necropsy material in the pathology department of the Christian Medical College Hospital, Vellore. The material is from all the necropsy examinations done in cases of stillbirths and neonatal deaths in the years 1951 to 1955 inclusive. For the purposes of this study we have included infants dying up to 3 months of age as neonatal deaths. Though this differs from the generally accepted statistical definition, it does help to give a broader picture of the problems of infant mortality.

Studies of this type are indicated in view of the high infant mortality rate in India. According to Chandrasekhar,[1] of all babies born nearly one-fifth die within the first year of life and about one-tenth within the first month. In 1955 the infant mortality for the North Arcot District in which Vellore is situated was 120.22 per 1,000. Coincident with the advances in family planning is quite naturally an interest in lowering infant mortality.

The Christian Medical College Hospital is a teaching general hospital of about 600 beds. This includes a maternity and pediatric service. About 98 per cent of the patients are from South India, and these represent in general the lower middle class of the population. During the five-year period of study there were 215 postmortem examinations in cases of stillbirths and neonatal deaths, defined as stated above. During this same period there were in the hospital 562 stillbirths and 423 babies dying in the first 3 months of life (382 in the first 28 days). Thus necropsy examinations were performed in 36 per cent of the neonatal deaths and in 11 per cent of the stillbirths. In studying the material, we have organized the cases according to both morbid anatomy and clinicopathologic correlation. It is difficult to arrive at an entirely satisfactory arrangement, and the one we have used is one of convenience, in which we have listed the cases (Table I) under the principal or predominant pathologic lesion which in most instances was at least the principal cause of death. In the event that there was a specific pathologic entity such as congenital malformation, we have for purposes of summarizing placed the case under this specific pathologic lesion even though there may be another lesion such as pneumonia which actually caused death.

STILLBIRTHS

The first 37 patients noted in Table I represent a group in which there was

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From the Departments of Pathology and Pediatrics of the Christian Medical College Hospital, Vellore, S. India.

Presented at the Third International Congress of Clinical Pathology, Brussels, July, 1957.

TABLE I

Antenatal and intranatal deaths (stillbirths) including anoxia but excluding specific entities	37
(Stillbirths listed under specific lesions, 24)	
Prematurity (exclusive of specific lesions except anoxia	29
Pneumonia (primary lesions)	45
(Associated with other lesions, 20)	
Miscellaneous respiratory pathology	10
Other infections	28
Intracranial hemorrhage	22
Congenital abnormalities (other than insignificant incidental anomalies)	31
Miscellaneous	13
Total	215

no significant pathologic lesion except for increased aspirated vernix or petechial (or larger) hemorrhages throughout the viscera but especially in the subpericardial and subpleural areas. Seventeen of the 37 weighed under 2,500 grams. This stillbirth group is one in which clinicopathologic correlation would seem to be even more essential than in any other group of this study.

TABLE II. STILLBIRTHS

No specific lesion other than anoxia		*37*
Macerated	12	
Excessive vernix in lungs	14	
Petechial hemorrhages in organs	12	
Maternal cause for asphyxia	15	
Toxemia of mother	4	

As seen in Table II there was evidence of asphyxia in the majority, taking the clinical history as well as petechial hemorrhage and increased pulmonary vernix as evidence of antenatal or intranatal anoxia. The presence of excessive vernix is admittedly a subjective finding, but in studying the lungs there were 14 in which there was an excessive amount of amniotic debris present. Several more showed what might be said to be a slight increase. For evidence of petechial hemorrhages we have had to rely on the autopsy protocols which, in some cases, were not in as complete detail in this regard as might be desired; and we did not find it possible to distinguish the size of the petechiae or ecchymoses from the written description. As regards maternal history, we found that in 15 cases there was clinical evidence for anoxia. This group includes such conditions as ruptured uterus, ante-partum hemorrhage, prolapsed cord, difficult labor, and others.

Twelve infants were definitely macerated and in 5 of these there was excessive vernix in the potential air spaces. Four of the mothers had definite evidence of toxemia of pregnancy. In the stillborn infants born to the 4 patients with toxemia, 2 were macerated fetuses. Altogether there were 29 cases out of the 37 which showed *anoxia if we consider one or* more of the following items as indicative of anoxia or asphyxia: (1) excessive vernix aspirate in lungs; (2) petechial hemorrhages in the viscera; (3) *a maternal or birth history* consistent with asphyxia.

In addition to these 37 stillbirths there were 24 more cases of stillbirth, which we have listed, however, in separate categories because of pathologic lesions of a specific nature. In 8 cases there was some intracranial hemorrhage and hence *these are described* in that section. There were 4 cases with a well-developed pneumonia. There were also 6 cases with congenital defects. One of these was an interventricular septal defect, and though the heart lesion cannot explain the antenatal death, we have listed it with the congenital heart lesions. Three of the cases of congenital syphilis which we studied as well as a case of full-term abdominal pregnancy were stillbirths.

PREMATURITY

This perhaps represents the most unsatisfactory group from the standpoint of classification. In the first place the definition of prematurity in this area is not standardized. In our hospital the weight of the normal full-term child is 6¼ pounds which is definitely less than that in Western countries and indicates that the figure of 2,500 grams which we have used as the dividing line for prematurity is perhaps too high. The group of 29 cases labeled prematurity in Table I represents those in which no specific pathologic entities were found. Some were very small and of apparent pre-viable size. Others were larger, but no adequate cause of death could be found. It is very likely that if in some cases better histories and protocols were obtainable and in some others more tissues could be studied, the group showing no lesions would be smaller. There are other factors such as dietary backgrounds of many of the mothers that may be related to infant mortality and yet be hard to assess.

In the group of premature infants, there were 7 multiple births; 10 had birth weights of 1,000 grams or less; 5 more had birth weights of more than 1,000 grams but less than 1,200 grams. In one of this latter group the lungs were extremely immature. Of the remaining 14 which were of larger size, there was one with asphyxia due to aspirated vomitus; the mothers of two had toxemia of pregnancy; another infant was born to a mother with an anemia of 4.5 Gm. per 100 ml.

PNEUMONIA

As seen in Table I, pneumonia is the outstanding pathologic process found in the over-all study. In delimiting this group, we have made the diagnosis of pneumonia only in cases showing significant numbers of neutrophils in the alveolar spaces. Those with congestion of the alveolar walls and neutrophils in the capillaries were not considered as pneumonia. No histologic diagnosis of interstitial pneumonitis was made and there were no cases showing giant cell or inclusion pneumonia. No cases of plasmacellular interstitial pneumonitis (Pneumocystis pneumonitis) as described by Hamperl[2] were found. In most of these cases of the entire series our study of lungs was limited to one or two sections, and in some no lung sections were available. As the pneumonitis process was often patchy, it can quite reasonably be assumed that if more sections had been taken for histologic study, pneumonia would have been diagnosed more frequently.

There was a number in which the infection apparently began in utero (Figs. 1 and 2). Table III shows the number of pneumonias (21) that we have included as being undoubtedly as well as possibly of intrauterine origin. In 3 of the stillborn infants and 3 of those dying shortly after birth there was definite increase in aspirated amniotic debris. In the group of 13 dying one to three days after birth, 4 showed what was definitely increased amniotic aspirate. In 4 of the 13 infants with pneumonia dying one to three days

TABLE III. PNEUMONIAS OF POSSIBLE INTRAUTERINE ORIGIN

Stillborn	4
Ten hours or less of postnatal life	4
One to 3 days, postnatal life	13

after birth the pneumonia was in addition to another important pathologic process. This rather high incidence of pulmonary infections of apparent intrauterine origin is no doubt related to the poor antenatal care and environment of many of the mothers.

The picture of the pneumonias in older infants varied from minimal to diffuse or extensive involvement. There

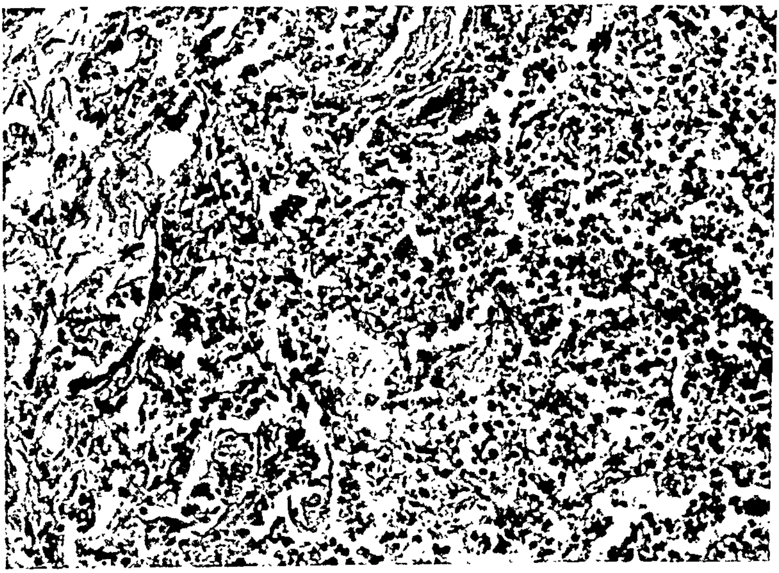

Fig. 1.—Pneumonia in stillborn infant. There was a difficult labor due to transverse arrest. The membranes had been leaking 3 days before delivery. Note the aspirated vernix material together with neutrophilic infiltration of the air spaces. (Hematoxylin and eosin; ×230.)

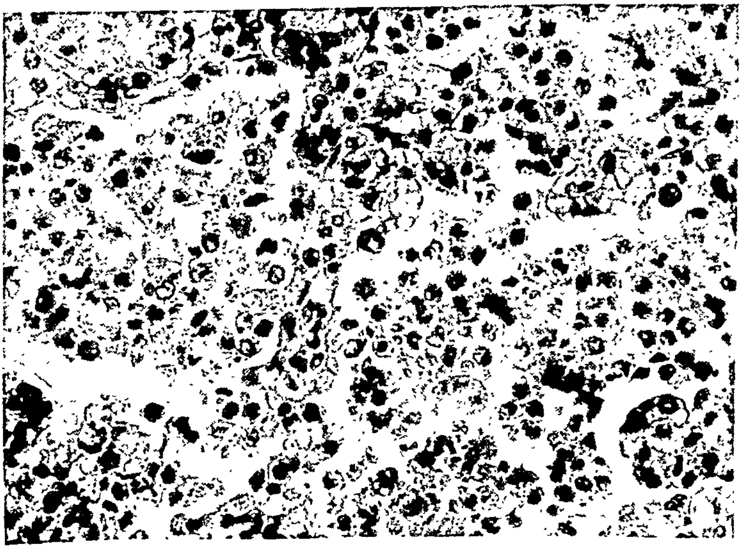

Fig. 2.—Pneumonia in child dying 10 hours after birth. (Hematoxylin and eosin; ×488.)

was a number in which there were only small foci of alveolar spaces containing neutrophils. Others showed diffuse infiltration of the air spaces with acute inflammatory cells.

There were 16 in which a necrotizing process was seen (Fig 3). Though in 1 or 2 the process might be thought of as a suppurative or abscess-forming pneumonia of the type seen in staphylococcic pneumonias, most of them represent what appears to be an entirely different process. There were degrees of destruction of the architecture of the lung varying from a basophilic smudging of the lung structure to that of complete necrosis or abscess formation. In most there was a basophilic amorphous debrislike material which in distribution and appearance resembled aspirated matter. In 9 of the 16 cases showing a necrotizing process basophilic material was found in the bronchial lumina as well as in the alveolar spaces. The neutrophilic reaction varied and in one in which there was a characteristic necrotizing lesion there was no significant polymorphonuclear response. On the whole, the neutrophilic response was relatively minimal compared with that in ordinary bronchopneumonia. In 3 of the cases there was a definite history of cyanosis following vomiting. Of the 16 infants with a necrotizing process as described, 11 weighed less than 2,500 grams at birth. One also had cancrum oris.

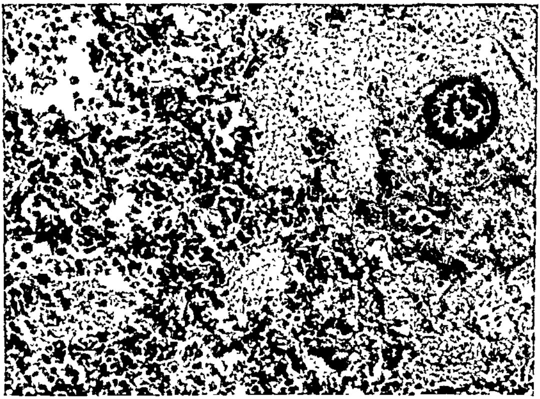

Fig. 3.—Necrotizing pneumonia in 4-day-old infant who had congenital ectodermal dysplasia. Note the necrosis and amorphous debris together with neutrophils in adjacent alveolar spaces. (Hematoxylin and eosin; ×244.)

OTHER PULMONARY LESIONS

Hyaline membrane disease was found in only one infant in the series. The child was born by cesarean section and weighed 4 pounds 2 ounces at birth. A considerable quantity of fluid was sucked from the throat and the baby was a little drowsy after the first cry. Oxygen was administered by nasal catheter. The child showed retraction of the intercostal spaces and was later put into an oxygen tent. Death occurred after 37½ hours of life.

Pulmonary hemorrhage was a hard problem to assess as a causative lesion accounting for death. In the first place, we usually had to rely on one or two histologic sections taken at necropsy examination, and no pattern was used as to number taken or sites selected. In 8 the hemorrhage was thought to be of sufficient severity to account for death. The extravasation of red cells was largely intra-alveolar, although it was also seen in areas involving the interstitial tissue and subpleural areas. In some there were a few scattered neutrophils. In an additional case there was pulmonary hemorrhage associated with a tetralogy of Fallot. The cause of death in this case was undoubtedly the pulmonary hemorrhage, but we have placed it in the other category. Aside from these there were several others with some degree of pulmonary hemorrhage but which we thought was not sufficiently severe to be related significantly to the cause of death.

A large amount of aspirated amniotic debris in the lungs sufficient to interfere with respiration was apparently the cause of death in an infant who died 12 hours after birth and in whom there was no other significant lesion. Aside from this case a number of others had a large amount of vernix material in the lungs, but though this may have been severe enough to have interfered with life, the infants had other pathologic entities of interesting or serious nature and have been listed (Table I) in that category. In some of the stillborn infants and in some of the cases of pneumonias of intrauterine origin, as mentioned, there was excessive amniotic aspirate in the air spaces.

MISCELLANEOUS INFECTIOUS DISEASE

As seen in Table I, there were 28 cases with infection other than pneumonia. There were 4 autopsies showing meningitis (ages of infants at death were 8 days, 15 days, 17 days, and 3 months, respectively), all of which were secondary to otitis media. In addition to these cases of meningitis, otitis media was present in 3 others and was apparently primarily responsible for their death.

Widespread sepsis was found in 4 infants at post-mortem examination. In 2 of these the site of infection was apparently through an infected umbilicus. In one of these the umbilical cord had been cut by an untrained village midwife (barber woman) using a kitchen knife. Later, after the cord had fallen off, a snuff dressing was applied.

In 4 infants the diagnosis of congenital syphilis was established; in 3 spirochetes were demonstrated in the tissues. The other showed typical histologic findings. Three were stillborn; one died after a few minutes.

Death was felt to be due to enteritis in 11 cases. In 5 of these there was histologic evidence of inflammation in the bowel wall. In the others no evidence of inflammation was found (in 2, no bowel sections were available).

One child died of peritonitis resulting from a traumatic perforation of the rectum which had been produced by a barber woman who had attempted to dilate the rectum.

One child had clinical tetanus, presumably from an infected umbilical stump.

INTRACRANIAL HEMORRHAGE

There were 31 cases showing intracranial hemorrhage. As seen in Table I we have divided these into 22 in which hemorrhage was the most prominent lesion and 9 others where the hemorrhage was in addition to another significant process. In this group of 9, the intracranial hemorrhage was presumably of secondary importance except in one case of imperforate anus and urogenital defect where there was extensive subdural and subarachnoid hemorrhage but which we have listed under the congenital abnormalities for purposes of classification. Other lesions were pneumonia, 4 cases; congenital cerebral defect, hyaline membrane disease, enteritis, and sepsis, 1 each.

Taking together the group of 22 in which the intracranial hemorrhage was the most significant lesion, we found that in 11 the history and findings would point to birth trauma as the cause of the extravasation of blood. In 6 cases, because of the history or the finding of excessive amniotic or meconium aspirate, we felt the cause was most consistent with anoxia. In this latter group of 6 cases the hemorrhage was apparently subarachnoid in 5; the other was described as blood on the tentorium. In the group of 11 apparently due to birth trauma there were 3 with a tear of the falx, 1 with a tear of the tentorium. Three were described as having tearing of the vein of Galen. In one of the last group there was also apparent tearing of veins entering the superior sagittal sinus. Aside from these obvious tears there were hemorrhages described as subdural in 3 cases and as extradural in 1. In addition to those due to birth trauma and anoxia there were 5 other cases. One showed hemorrhage into the lateral ventricles. This was a premature child on which Willet's forceps had been used. In another the autopsy record described fluid blood in the posterior cranial fossa. The child was a 4,050 gram stillborn baby of a diabetic mother. Of the remaining 3, 2 were described as apparently having subarachnoid hemorrhage without obvious lesion, the other had subdural and subarachnoid hemorrhage. Of this group of 22 infants in whom the central nervous system hemorrhage was the major lesion, 8 were stillborn. In 2 the heart was beating but the infant did not breathe; another lived but a few minutes. Aside from one infant living for 8 days, none lived more than 5 days after birth.

CONGENITAL ABNORMALITIES

In Table IV are outlined the 31 cases listed as "congenital abnormalities."

In the group listed as "multiple congenital defects" were the following abnormalities:

One infant had a bizarre urogenital abnormality in which the vagina, urethra, and large bowel opened into a common structure which emptied through the usual urethral orifice. There was duplication of the vagina and uterus.

In another case there was an absent left adrenal gland and kidney as well as a unicornuate uterus. This child weighed 2 pounds 8 ounces at birth and died at 1 day of age. Aspirated vernix was abundant in the lungs.

Another child showed a combination of hydrocephalus, esophageal atresia, and abnormal ears.

was later put into an oxygen tent. Death occurred after 37½ hours of life.

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One child had clinical tetanus, presumably from an infected umbilical stump.

One of the skin diseases was clinically a congenital ectodermal dysplasia. The child had a necrotizing pneumonia. The other child with a dermatologic lesion was a 12-day-old female who had ulceration of the mouth and cheek together with bullae on the buttocks. There was obvious malnutrition.

The child on whom a craniotomy was done as a destructive procedure showed no demonstrable lesion.

The abdominal pregnancy was a 2,600 gram infant who had died before surgery was done.

There was only one case of erythroblastosis. The child was a stillborn female weighing 5 pounds 12 ounces. This infant represented the fifteenth pregnancy of the mother. Babies born of the eleventh, twelfth, and thirteenth pregnancies were jaundiced; the previous (fourteenth pregnancy) baby was a hydrops. The mother was group AB Rh_0 negative and had anti-C and anti-D antibodies.

Several cases showed hepatic lesions. Only one was listed as a case in which the primary lesion was liver disease. This was a 2-day-old baby born of a mother with eclampsia and showed marked vacuolization of liver cells, presumably a severe fatty change. Another infant showed also a very severe fatty change. This child is noted under intracranial hemorrhage and was stillborn. Two of the infants dying with pneumonia, one of Meckel's diverticulum with volvulus, and a case of meningitis also showed significant fatty change in the liver. There were two cases with peculiar areas of focal necrosis. These are listed elsewhere under intracranial hemorrhage and pulmonary hemorrhage. Another case showing liver pathology was mentioned under congenital abnormalities. This liver showed only very occasional bile ducts in the periportal spaces.

The sacral teratoma showed a typical picture and was present in a child dying at 10 days of age with a necrotizing pneumonia.

In the 3 cases in which we could find no specific pathological condition and cannot classify, one possibly had a septicemia. The other 2 died at 5 days and 2 days of age, respectively. Both had histories consistent with some asphyxia at birth.

DISCUSSION

A study of this type obviously takes up only part of the problems of infant mortality. It would be well to be able to investigate the home environment of the mothers. The nutrition background and the manipulations and treatment by unskilled midwives (barber women) no doubt greatly influence the infant mortality in this area. History of antenatal care and the procedures prior to hospital entry are generally not available.

The spectrum of pathological entities probably reflects this background in the fact that the predominant cause of death in the neonatal period is infectious disease, especially pneumonia. The rather large group of pneumonias of intrauterine origin is indicative of the fact that if antenatal care were improved, the infant mortality would no doubt decrease. Furthermore the data we have reviewed do not necessarily accurately mirror the true situation as regards childbirth, for most of the infants on the newborn service are born in this hospital whereas hospital births are only a small segment of the deliveries in India.

We cannot explain the rarity of hyaline membrane disease. Erythroblastosis is apparently quite rare though occasionally seen clinically. Intracranial hemorrhage was quite common in our series and is probably related in part to maternal conditions such as contracted pelves and other problems. The habit of cutting and tying the umbilical cord with unsterile objects must certainly account for some cases of sepsis and tetanus.

We doubt if it is possible to draw any conclusions as to the relative incidence of congenital defects in babies born in this area.

SUMMARY

A study was made of the findings in 215 consecutive necropsy examinations in cases of stillbirths and neonatal deaths at the Christian Medical College, Vellore, South India. The primary pathologic conditions associated with or causing death are tabulated. Pneumonia is the principal cause of death. Anoxia due to maternal causes, intracranial hemorrhage, and other infectious disease are also common. Such conditions as erythroblastosis and hyaline membrane disease are rare. The study points to the fact that the answer to most of the problems of infant mortality is in antenatal and perinatal care.

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THE NECK-RIGHTING REFLEX IN CHILDREN

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THE neck-righting reflex was first demonstrated by Magnus in certain infra-human mammals.[1] The reflex is one of many postural reflexes which permit an animal to assume and maintain an upright position. The reflex orients the body in relation to the head, and can be seen when a cat is dropped blindfolded with its legs pointing upward. With great speed the animal turns its entire body and lands on all fours. Magnus observed that first the head is brought into the upright position by means of labyrinthine righting reflexes. Then follows the neck-righting reflex in which the upper half of the body turns, bringing it into direct alignment with the head. By means of the body-righting reflex the lower half of the body then turns and the entire body lands in the upright position.

The neck-righting reflex is not easily observed in man. Schaltenbrand, however, attempted to demonstrate the existence of this reflex in human infants.[2, 3] In Ford's[4] textbook of pediatric neurology the neck-righting reflex is described after Schaltenbrand as a normal reflex in infants and children. The presumed existence of this reflex in infants and children has been cited as the physiological basis for the "whirling" phenomenon, a clinical test in child psychiatry.[5, 6*] This note deals with an attempt to confirm Schaltenbrand's original work.

According to Schaltenbrand, a typical neck-righting response, as described by Magnus, can be seen with great frequency in human infants. He believed that the response disappeared at about 5 years of age. His observations were based on a study of 122 children ranging in ages from birth to 5 years. In his study, ". . . the child is placed flat on his back and the head is turned 90 degrees to the right or left. There follows a reflected torsion of the vertebral column in the same direction as the induced rotation of the neck." Schaltenbrand's data, together with our own, may be seen in Table I.

SUBJECTS AND METHODS

One hundred children at Bellevue Hospital were studied. Twenty were from 1 to 7 days old. The rest ranged in age from 2 weeks to 5 years and were observed in the Well Baby Clinic and the regular Pediatric Out-Patient Department. The majority of the subjects were neither seriously nor chronically ill.

Each child was examined while lying on his back. Using both hands, the examiner grasped the child's head at the temples (Fig. 1, *A*). The head was gently turned, first 90 degrees to one side and then 90 degrees to the other side. The head was held for a minimum of 5 seconds in each position. Schaltenbrand does not state the time during which the child's head was held in the lateral position, nor does he define a "questionable" response.

In this study a response was considered positive if, within 5 seconds

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*We have evaluated this test elsewhere.[7]

after the head was turned 90 degrees to either side, the child turned his trunk in the same direction (Fig. 1, *B*). The arbitrary period of 5 seconds was adopted because it was felt that any response of greater latency should not be considered a reflex. If there was a partial turning of the trunk in the direction of the head within the 5-second period, the response was recorded as questionable. Any other response was considered negative (Fig. 1, *C*).

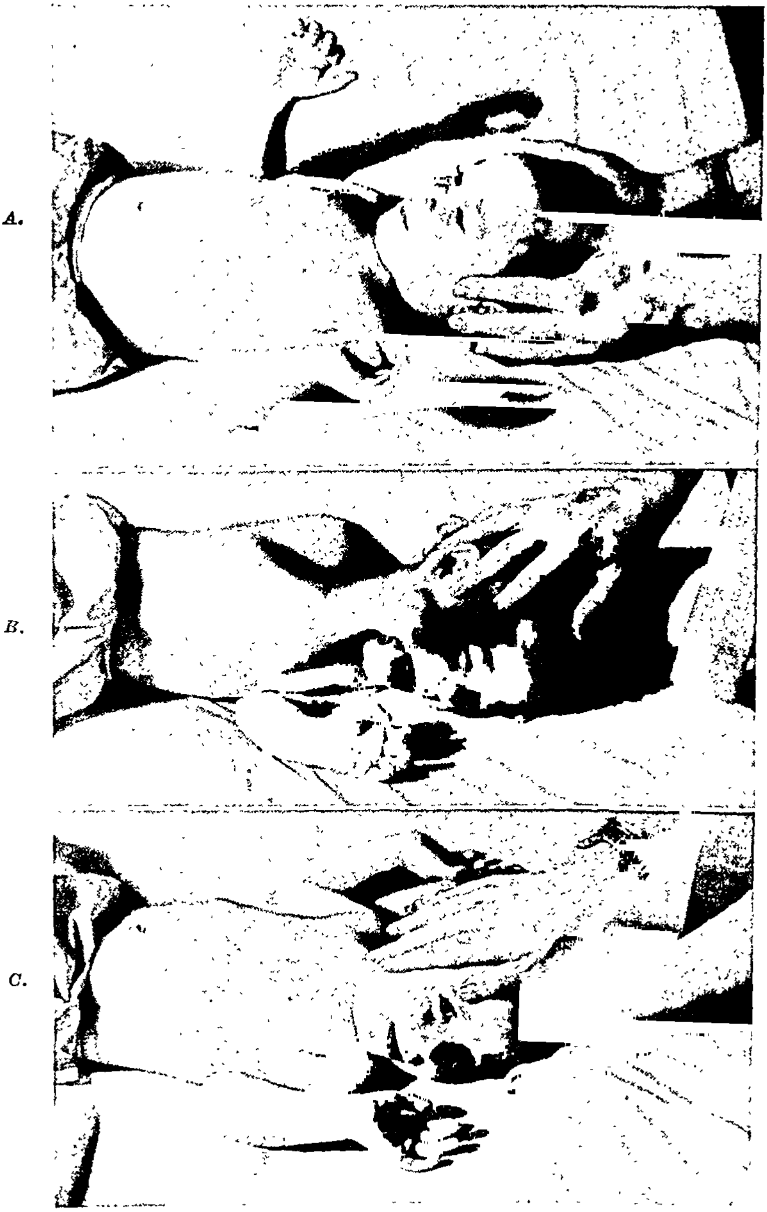

Fig. 1.—Neck-righting reflex. *A*, Starting position; *B*, positive response; *C*, negative response.

RESULTS

Our results are shown in Table I.

TABLE I. NECK-RIGHTING RESPONSE IN CHILDREN

	PRESENT STUDY (NUMBER OF CASES)	SCHALTENBRAND[3] (NUMBER OF CASES)
Children tested	100	122
Positive	6 (6%)	83 (68%)
Questionable	8 (8%)	25 (20%)

About one-third of the children were upset by the test and cried or thrashed about either before, during, or after the turning of the head. Of the 100 children tested, 6 showed a positive response and 8 a questionable response. These children ranged in age from 1 month to 4 years, with no age trend. It is noteworthy that of these 14 children, 10 were crying and struggling during the test. Frequently a child who showed a positive response would not do so if the examiner waited until the child stopped crying. In some of the children with positive responses, the response was present in turning of the head in one direction only, or disappeared with repeated turning of the head.

CONCLUSION

Our results differ clearly from those reported by Schaltenbrand. It is difficult to account for this discrepancy. Perhaps Schaltenbrand held his subject's head in the lateral position for long periods (30 to 60 seconds). Another possibility is that a large number of the children he examined were crying and struggling during the test. When a child's head is passively rotated 90 degrees to the side, he is likely to turn his body and align it with his head at some time during a long period of struggling. In any case, a prompt rotation of the trunk in response to the turning of the head is seen only occasionally in children up to the age of 5 years and is usually associated with crying and struggling.

Under these conditions it is difficult to conceive of the response described by Schaltenbrand, even when present, as a reflex in the usual sense of the term. The response is not uniformly seen in all members of the species in question; it does not occur with short latency, nor does it recur regularly as testing is repeated.

SUMMARY

An attempt was made to reproduce the work of Schaltenbrand pertaining to the neck-righting reflex in infants. One hundred children ranging from newborn infants to 5 years of age were examined. Contrary to the results of Schaltenbrand, the response was observed in a small number of cases only and was generally associated with crying and struggling.

We are grateful to Dr. Harry Bakwin and Dr. Hans-Lukas Teuber for many valuable suggestions.

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ACNE. A NEW APPROACH TO AN OLD PROBLEM

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ACNE is the scourge of youth.[1] Too many parents believe that it has to "run its course" and there is not much to be gained in its treatment. Unfortunately this neglect sometimes extends to physicians with teen-age patients who consult them for other ailments and may be afflicted also with acne vulgaris. It is inexcusable to dismiss lightly the harmful emotional trauma, inferiority complexes, and personality defects which acne imposes upon its young victims, not only during the active course of the disease but even when it has been outgrown and disfiguring scars remain. Every patient with acne seen by general practitioners should be encouraged to undergo treatment. Its benefits should be described and the results of neglect emphasized. Treatment should be simple and yet effective. Such a treatment routine is the subject of this report.

To better describe the requirements for adequate treatment the physiological implications in acne vulgaris will be reviewed briefly. Acne is a physiologic reaction in the skin due to hormonal changes occurring at adolescence. In the male it is associated with the increase in androgens and in the female in progesterone. These hormones stimulate the sebaceous glands, causing an increase in the production of sebum. The primary pathologic change is a plugging of the follicular orifice by a mixture of keratin and sebum, causing the formation of the earliest acneform lesion, the comedo. Pores are also closed up by a simple epithelial overgrowth giving rise to papules. Damming of the follicular orifice, with continued sebum-secreting activity of the sebaceous glands, increases pressure within the comedo with eventual rupture of the follicular wall. Inflammatory changes occur in the corium on which the sebum and keratin react as a foreign body or, in the presence of bacteria, give rise to secondary infection. The formation of acneform lesions is depicted in Figs. 1 to 4. "It can be seen that a blend of foreign body reaction and bacterial infection, all secondary to follicular rupture, explains much if not all of the clinical changes in acne."[2]

During the early stages, acneform lesions are primarily comedones and noninflammatory papules. Oily skin and seborrhea capitis are often associated. The severity of acne increases with the onset of inflammation and infection. Superficial or deeper nodules, cysts, pustules, and abscesses are superimposed upon the oily, comedone skin.

Since the comedo is the primary acne lesion, treatment should be aimed at preventing the formation of new comedones, removing those already present, and preventing infection. In the more severe forms, treatment by

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the dermatologist should also include means of slowing down the activity of the sebaceous glands, of combating infection actively, and, in a few selected cases, of modifying the hormonal balance responsible for the difficulty in the first place.

In recent years the acne patient has been treated with vitamins, hormones, antibiotics, restrictive diets, x-ray, ultraviolet and quartz lamps, cryotherapy, vaccines, surgery, and a host of topically applied concoctions. Eventually it was realized that the most useful regimen of therapy in acne vulgaris consists of a mildly restricted diet, local applications designed to dry, peel, and degerm the skin, judicious expression of comedones, and evacuation of pustules. X-ray, systemic antibiotics, hormonal therapy, cryotherapy, and vaccines are useful

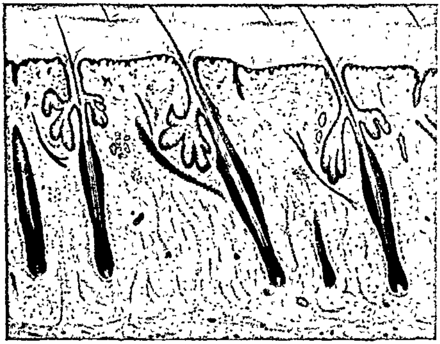

Fig. 1.—Normal skin.

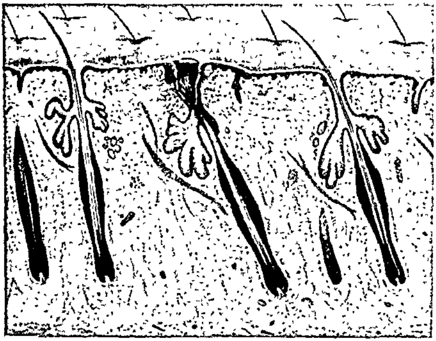

Fig 2.—Follicular orifice plugged by a comedo.

when they are restricted to selected cases which would not properly respond to the more simple measures. "Thus the main body of our therapeutic armamentarium is still local treatment on an empirical basis as it has been practiced for almost 100 years. . . ."[3]

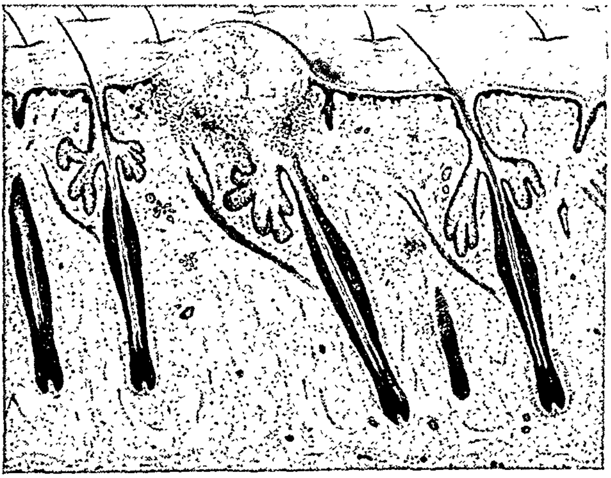

Fig. 3.—Development of pustule.

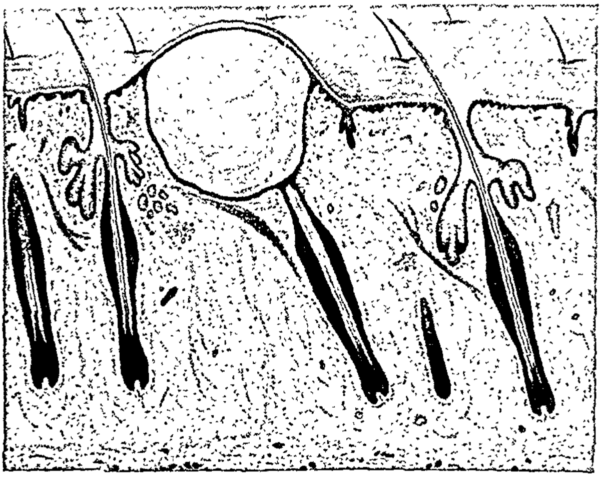

Fig. 4.—Cyst formation.

THE NEW TREATMENT ROUTINE

Most acne vulgaris patients seen by the physician can be practically and effectively treated by him with a simple therapeutic routine employing a mildly restricted diet, simple acne surgery, and new, easy-to-use antiseborrheic medications recently described by Robinson,[4] Finnerty,[5] Howell,[6] and Schmitt.[7] It is assumed, of course, that the physician takes whatever measures are necessary to improve the general health in each individual case.

Diet.—Severe dietary restrictions are unnecessary and would not be adhered to anyway. Vitamin supplements, especially vitamin A, should be prescribed if, in the judgement of the physician, their intake by the individual patient is deficient.

The patient should be told to avoid excess carbohydrates (with emphasis on candy and carbonated beverages—especially cola drinks), chocolate, nuts, peanut butter, pork, and fried foods. When milk or milk products are ingested excessively, they should be curtailed. Advice should be given on a liberal diet rich in lean meats, fruits, vegetables, and vitamins.

Local Treatment.—There are many useful local medications available. These usually contain combinations of sulfur, salicylic acid, and resorcinol in nongreasy, water-dispersible bases. However, during the past year we have observed that most of the desired effects of local medication could be obtained by the sole use of a new lathering cream* for the therapeutic washing of the skin (instead of using soap). The therapeutic activity of this cream is primarily supplied by a combination of surface active wetting and cleansing agents: sodium dioctyl sulfosuccinate, sodium alkyl aryl polyether sulfonate, and sodium lauryl sulfoacetate. Drying and keratolytic powers are enhanced and strong antibacterial properties supplied by 2 per cent salicylic acid, 2 per cent micropulverized sulfur, and 1 per cent hexachlorophene.

The therapeutic skin wash is preferable to other local medications because it accomplishes desired results without the necessity of applying and leaving on the skin layers of medication which many teen-agers (especially boys) object to. The patient washes his face twice a day using the lathering cream (instead of soap). The lather is massaged into the skin for five minutes and then rinsed off thoroughly. If any residue is incompletely rinsed off it may cause chapping of the skin. We have found it important to emphasize the need for massaging the lather into the face for a full five minutes as teen-agers are prone to forget that the therapeutic washing of the skin is a treatment and not merely a means to keep the face clean.

Dandruff and excessive oiliness of the scalp are frequently seen in acne vulgaris patients. These should be treated using the same lathering cream as a therapeutic shampoo. A small amount of the cream is rubbed into the wet scalp, working up a lather for five minutes. It is then rinsed off and the shampoo is repeated, rubbing the lather into the scalp another five minutes before thorough rinsing.

Acne Surgery.—The manual expression of comedones should be performed by the physician using one of the mechanical devices available for this purpose. Squeezing of comedones or pustules with the fingers (a common error of the acne patient) should be emphatically cautioned against.

Abscesses and cysts should be opened by superficial incisions using a needle, cataract knife, or small pointed Bard-Parker blade. Care should be taken that these incisions do not cause additional scarring.

Clinical Evaluation of Fostex Cream.—The treatment routine described above was used in 371 cases of acne vulgaris, of which 133 cases were classified as severe and 238 as moderate

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*Fostex Cream, Westwood Pharmaceuticals, Buffalo, N. Y.

Female patients numbered 227 and male 144. Fifty-nine patients were under 15 years of age, 241 were between 15 and 25, and 71 were over 25 years old.

In the severe cases, the routine of simple diet, therapeutic washing and acne surgery was supplemented as individually indicated by:

1. X-ray used at times with caution to suppress activity of the sebaceous glands, thereby controlling the primary cause of the formation of acne lesions. Small doses of x-ray with a full realization of possible injurious results must be used discriminately.
2. Short courses of oral antibiotics for the control of acute infection.
3. Staphylococcus vaccines for the control of chronic infection.
4. Estrogenic hormones in girls over 18 years of age only when marked exacerbation of the acne was associated with menstruation.

RESULTS

The simplified treatment routine was found to improve every mild or moderate case of acne. Two or three days after initiating the use of the therapeutic facial scrub, the skin becomes dry and starts to peel. This tends to soften and loosen the keratin plugs and epithelial overgrowth blocking the pores. A marked reduction of the comedones ensues. Manual expression of the remaining comedones, by the physician, is facilitated especially if the patient rubs a small amount of the cream into the skin and covers it with a hot towel, for ten minutes previous to this manipulation.

In the severe cases, local treatment by washing the skin with the antiseborrheic cream was, in the author's opinion, instrumental in shortening the course of therapy. The skin was made dry and the lesions regressed sooner, in our experience, than before including the cream in our acne routine. When the acute phase of treatment was over, the patients continued using the antiseborrheic cream or the same formulation in cake form* as maintenance therapy—to prevent recurrences of the excessive oiliness and of the comedones.

Oily scalp and dandruff associated with acne were effectively controlled in every case by use of the antiseborrheic cream as a therapeutic shampoo. Maintenance of a clear scalp was possible by shampooing once weekly or less often.

In two blonde patients with dry skins the cream was found too drying and had to be discontinued. In a few other patients who scrubbed their faces too strenuously, or too often, chapping occurred. This was corrected by stopping the use of the cream for 2 or 3 days and resuming the therapeutic washing morning and night with less strenuous massaging of the lather into the skin.

In 1950 Dexter[8] reported excellent results in the treatment of acne vulgaris with a therapeutic regimen which could be easily adapted to any clinic or physician's office. Diet and topical therapy with a sulfur-resorcinol lotion were the mainstays of her acne routine. We, too, have found a similar routine adaptable to the general practitioner's office. However, the easier-to-use therapeutic skin wash achieves better patient cooperation, especially among boys who are adverse to daubing lotions on their faces. There is also an economic advantage to the effectiveness of the same medication as a therapeutic shampoo since many acne patients have to be treated for dandruff and oily scalp. Patients were invariably pleased with the esthetic qualities of this convenient shampoo.

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*Fostex Cake.

SUMMARY

A new, practical, and simple therapeutic regimen for acne vulgaris is described. Simple dietary discrimination and local skin therapy with a cream which is used as a wash and shampoo has been found effective in the treatment of most cases of acne vulgaris of the comedo-papular type. The regimen is also a valuable adjunct in severe cystic acne requiring additional individualized therapy.

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A 'Free' Translation

There are few medical maxims more truthful and salutary than that inculcated by the immortal Baglivi: "Scire multa, agere pauca," which may be freely translated, thus: "Let your knowledge, on all subjects, and especially of disease and its remedies, be thorough and complete; yet, beware of frequent and unnecessary interference with the recuperative efforts of nature."

FROM A DISSERTATION READ BEFORE THE NEW LONDON COUNTY MEDICAL SOCIETY IN 1854 BY ISAAC G. PORTER, M.D., OF NEW LONDON, CONNECTICUT.

MARCHESANI SYNDROME

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IN 1939 Marchesani[1] described four patients with short stature, brachydactyly, and spherophakia (small, spherical lens) with associated myopia and glaucoma. Since then ten additional cases have appeared,[2-7] for the most part in the foreign ophthalmological literature. Recently we observed two siblings who satisfy the criteria of the Marchesani syndrome. Since this syndrome has not been reported in the American pediatric literature, a presentation of their cases and review of the literature seemed indicated.

CASE REPORTS

CASE 1.—D. K., a 9-year-old boy of Irish extraction, was referred to the Bellevue Hospital Children's Cardiac Clinic in February, 1956, for evaluation of a murmur. He had led a normally active life and had never had cardiovascular symptoms. A murmur was heard at the age of 2 years, and since that time he had been observed in several hospitals until his admission to the Bellevue Hospital Children's Service for further evaluation of the murmur.

Poor eyesight was first observed at the age of 5, and one year later he entered the Manhattan Eye, Ear and Throat Hospital because of bilateral dislocated spherophakic lenses and secondary glaucoma.* A combined intracapsular cataract extraction was performed on the right eye with vitreous loss and iris prolapse. At a later date the child was readmitted for a combined intracapsular extraction and two-pillar iridencleisis on the left for relief of the high tension glaucoma. The tension remained normal for about a year, when it suddenly increased again and a left cyclodialysis was carried out. In 1956 retinal detachment was noted on the left and treated with diathermy. The vision on his last discharge was O.D. 20/70, O.S. 20/200.

Delivery had been normal at term, with a birth weight of 5 pounds. Motor and speech development was normal, and he was considered an average student. He had had measles, chicken pox, mumps and several uncomplicated ear infections. According to the mother he was "always small for his age." The mother was 31 years old, and the father 34 years of age. They were first cousins. She was short (4 feet 8 inches), weighed 138 pounds, was in good health, and her physical appearance was unremarkable. The father was 5 feet 4 inches, weighed 125 pounds, and was in good health. Both parents stated that their respective families were all short and a maternal uncle had short, stubby hands. The maternal grandmother had cataract extractions late in life. There was no family history of other serious eye defects or heart disease.

He was an alert, stocky child with thick corrective glasses. His blood pressure was 84/50 mm. Hg. The height was 44 inches and weight 45 pounds, which placed him below the third percentile group for his age (average for age: 54 inches and 65 pounds, respectively). Both eyes were aphakic with surgically altered pupils. Funduscopic examination showed mild cupping of the disc head. Finger tension of the

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From the Children's Medical Service, Bellevue Medical Center.

*A more detailed description of the ophthalmological findings will appear in a later report.

eyeballs was not strikingly increased. The precordium was not prominent. He had a regular sinus rhythm. The point of maximum impulse was in the fifth intercostal space on the mid-clavicular line. P_2 was diminished slightly but present. A moderately loud, coarse systolic murmur was heard over the entire precordium, maximal in the second and third intercostal spaces at the left sternal border. He had a broad stocky chest and body. The head seemed slightly flattened with a broad forehead. The hands were "spade-like" with broad thick palms and short stubby fingers; and he was unable to flex his fingers fully or to make a fist. The nails were convex but the ungual angle was not obliterated. The rest of the physical examination was within normal limits.

Laboratory Data.—Hemoglobin was 14 Gm. White blood count and differential count were normal. Routine urinalysis as well as amino acid assay was normal. The blood cholesterol was 177 mg. per cent, nonprotein nitrogen 31.6 mg. per cent. X-rays of the hands and wrists showed a markedly retarded carpal development (approximately that of a child 4 to 5 years old) and symmetrically shortened and thickened phalanges and metacarpals. The long bone and skull series revealed no changes.

Cardiac Investigation.—By fluoroscopy and two meter chest x-rays, there was no transverse enlargement but there were fullness of the right ventricular curve and slight lifting of the apex. Moderate pulsations of the pulmonary artery were observed, but the

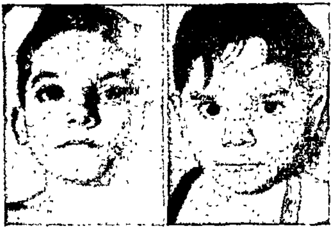

Fig. 1.

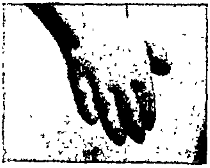

Fig. 2.

Fig. 1.—Patients D. K. and P. K.
Fig. 2.—Hand of P. K. (Case 1), showing brachydactyly.

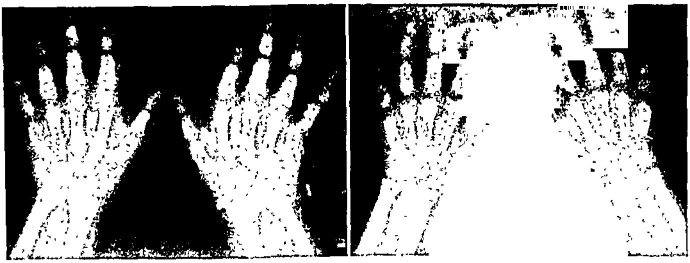

Fig. 3.—Roentgenograms of hands and wrists of patients D. K. and P. K., showing retarded ossification and short, wide phalanges and metacarpals.

peripheral lung fields seemed abnormally clear. The left anterior oblique view showed slight shelving of the right atrium, and the right ventricle appeared somewhat enlarged. The left ventricular contour was normal. In the right anterior oblique projection there was a suggestive concavity at the level of the right outflow tract. The electrocardiogram showed right deviation of the electrical axis and a vertical heart. P-R equaled 0.15 second, QRS equaled 0.07 second, and there were a peaked P wave in Lead II, and R-R′ in V_1 with an intrinsicoid deflection of 0.04 second.

On the basis of the location of the murmur, a diminished second pulmonic sound, evidence of right ventricular hypertrophy with increased clarity of the peripheral lung fields, a moderate pulmonary stenosis (probably infundibular) seemed the most likely diagnosis. The possibility of an associated atrial septal defect was also suggested.

Cardiac catheterization was carried out in February, 1957, and pressure and oxygen saturation values were obtained. The catheter could not be passed into the pulmonary artery and a sample could not be withdrawn from the right ventricular outflow tract (? infundibulum) perhaps because the tip of the catheter lumen was wedged against the muscle wall. A mild right ventricular hypertension of 47-38/7 mm. Hg indicated mild pulmonary stenosis, probably infundibular. Oxygen saturation studies were inconclusive as to the possible presence of a left-to-right shunt.

Case 2.—P. K., the 6-year-old brother of D. K., was referred to the Bellevue Children's Cardiac Clinic for evaluation of a cardiac murmur.

The child was fully active and free from cardiac symptoms. A murmur was first heard at 3 years of age. He was observed at another hospital for a year and no diagnosis known to the mother was made nor was activity restricted.

At the age of 5 years he was first seen at the Manhattan Eye, Ear and Throat Hospital and noted to have bilateral, subluxated spherophakic lens and mild glaucoma (tensions ranging from 20 to 46 mm.). In view of the poor surgical results in the older brother and the successful control of intraocular tension with the intermittent use of miotics, operation was not done. The high myopia (–17 diopters) was corrected to 20/100 O.U. with glasses.

The child had been delivered at term by elective forceps and weighed 5 pounds 5 ounces. There were no neonatal complications and the motor and speech development was normal. He was an average student. There had been no serious illnesses. The family history is given under Case 1.

The boy was very short, stockily built, and alert. He weighed 37 pounds and his height was 38 inches. (Mean weight for his age is 46 pounds, placing him just at the third percentile; average height is 46 inches, placing him below the third percentile.) The head was somewhat broad and flattened. The high myopia of the spherophakic lens prevented visualization of the fundus. On palpation of the eyeball the tension was not perceptibly increased. The chest was broad and muscular. Lungs were clear. The cardiac rhythm was regular. The point of maximal impulse was in the fifth intercostal space at the mid-clavicular line. A moderately loud, harsh, groaning systolic murmur was heard loudest in the supine position over the fourth interspace at the left sternal border and transmitted upward and slightly outward toward the apex. The abdomen was soft, and the liver and spleen could not be felt. The extremities seemed slightly short. The hands were "spadelike," with thick palms and short stubby fingers that could not be fully flexed. The nails were convex but the ungual angles were preserved. Neurological examination was negative. The hemoglobin was 11.0 Gm. and the white blood count was normal. Routine urinalysis and amino acid assay were normal. The nonprotein nitrogen was 33 mg. per cent and cholesterol was 177 mg. per cent.

X-rays of the skull and long bones were normal except for the carpal centers which were markedly retarded (at the 2-year level) and the metacarpals and phalanges which were short and thick. Chest films and fluoroscopy showed a normal cardiac contour. The electrocardiogram showed a regular sinus rhythm with no deviation of the electrical axis. Conduction times and precordial lead patterns were normal. The cardiac findings most likely represent a small ventricular septal defect although the quality of the murmur is slightly suggestive that it may prove to be a functional type.

REVIEW OF PREVIOUS CASES

Virtually all of the reports of the Marchesani Syndrome have appeared in the ophthalmological literature. This is not surprising inasmuch as the presenting symptoms are myopia and glaucoma. In review of the available cases it was immediately apparent that the ocular findings were described in extensive detail while the systemic changes were commented on briefly.

The first four cases described by Marchesani[1] were from two families. Three were siblings of normal parents, while the other single case was an offspring of short parents, one of which had "stubby hands."

Meyer and Holstein[2] reported four siblings born of short parents who were first cousins. Three of these children were virtually blind, two having had lens extractions.

Schmid[3] added one patient. Both parents were said to be small, with short extremities. A grandfather was also described as short, with "severe myopia."

In the patient described by Stadlin and Klein,[4] the parents were noted to be "brachymorphic," with normal eyes.

Rousseau and Hermann[5] described one family through four generations. The great-grandmother was short, with spherophakic lens but normal hands. All thirteen of her siblings had severe myopia. One of her daughters had the full syndrome, and six of this daughter's seven children were studied. One son had the characteristic eye changes and short stature but normal hands, while his daughter had the full syndrome. Two other siblings had severe myopia but had apparently normal lens and extremities. All others were normal. Thus there were two complete cases and two with eye changes only.

Seeleman[6] added one other patient whose parents were normal except for maternal myopia.

In 1952 Arjona[7] reported three cases from two families. One of the two from the first family had the full syndrome, the second had the eye changes and short hands, which were not, however, typical brachydactyly. The third, from the second family, had the eye changes but normal extremities. There was thus one definite "full" syndrome and two others with eye changes only.

Our two new cases represent the only two offsprings of two short parents who were first cousins; a maternal grandmother was short, wore glasses all her life, and had cataract extractions late in life.

In Tables I and II are summarized the sixteen cases thus far reported showing spherophakia, short stature and extremities, and brachydactyly. It is hardly meaningful to use percentages in such a small series. It can be seen that fourteen patients suffered from severe myopia, nine had glaucoma, and eight had subluxated lenses.

TABLE I

CASE AND SEX	AUTHOR	PARENTS	AGE OF ONSET OF EYE SYMPTOMS	EYES	STATURE	EXTREMITIES
1. S. H. Male	Marchesani	Father: small, short hands and normal eyes Mother: small, normal hands and eyes	8 yr.	Bilateral microphakia and subluxation into anterior chamber; glaucoma; T—50 mm. O.U.	Broad chest and full muscles; height at 8 yr., 108 cm.	Short extremities, brachydactyly, marked carpal retardation with 3 centers at 8 yr.
2. R. J. Female	Marchesani	Normal	--	Bilateral microphakia, iridodonesis, and myopia; T—30 to 35 mm. O.U.	Broad chest with heavy musculature; height at age 36 yr., 147 cm.	Short extremities with brachydactyly
3. M. R. Male	Marchesani	Normal (same as Case 2)	--	Bilateral spherophakia, iridodonesis, and myopia. Tension normal	Broad frame and heavy musculature; height at age 38 yr., 156 cm.	Short extremities with brachydactyly
4. G. A. Female	Marchesani	Normal (same as Case 2)	--	Bilateral spherophakia, iridodonesis, and myopia. Tension not mentioned	Broad frame and heavy musculature; height at age 33 yr., 153 cm.	Short extremities with brachydactyly
5. M. B. Female	Meyer and Holstein	First cousins, both short (4′ 10″ and 5′ 4″) with normal eyes	13 yr.	Bilateral spherophakia with subluxation O.D.: T—82 mm., lens extraction, subsequent retinal detachment, light perception only and tension still high O.S.: T—82 mm., deep glaucomatous cupping. Vision 4/200	Muscular; height at age 17 yr., 4′ 6″	Short extremities, with brachydactyly
6. G. B. Female	Meyer and Holstein	Same as Case 5	7 yr.	Bilateral spherophakia, subluxation and iridodonesis O.D.: T—24 mm. Vision 16/200 O.S.: T—12.5 mm. Vision 16/200	Short and muscular; height at 26 yr., 4′ 7″	Brachydactyly

7. W. B. Female	Meyer and Holstein	Same as Case 5	9 yr.	Bilateral spherophakia, with presumed glaucoma, lens extraction, now only light perception O.D.: Corneal leukoma and atrophic iris O.S.: Marked iridodonesis with absent lens	Short and muscular; height at 23 yr., 4′ 6″	Brachydactyly
8. E. B. Male	Meyer and Holstein	Same as Case 5	9 yr.	Bilateral spherophakia, both lenses cataractous with no light perception; T—40 to 60 mm. O.U.	Short and muscular; height at 21 yr., 4′ 9″	Brachydactyly
9. Female	Schmid	Unrelated; both short	--	Bilateral spherophakia and subluxation, lens extraction O.D.: Tension 24 mm. O.U. Vision 1.5/50 O.U.	Height at age 17 yr., 158 cm.	Brachydactyly
10. L. F. Female	Stadlin and Klein	Parents and sister "brachymorphic" with apparently normal eyes	6 yr.	Bilateral microphakia, subluxation, and myopia (–20 diopters), tension not mentioned, nystagmus and paralysis of upward gaze	Full musculature; height at 20 yr., 160 cm.	Short extremities and brachydactyly
11. Female	Rousseau and Hermann	Mother short with bilateral spherophakia, subluxation, and glaucoma, but normal hands	--	Bilateral spherophakia and glaucoma O.S.: light perception only O.D.: detached retina, vision 1/10	Height at 37 yr., 148 cm.	Short extremities, stubby feet, and brachydactyly
12. Female	Rousseau and Hermann	Father, son of Case 11 O.D.: subluxated, microphakic lens extracted O.S.: severe myopia, extremities normal	--	Bilateral microphakia and severe myopia	"Short"	Brachydactyly
13. Female	Seeleman	Normal except mother *myopic*	9 mo.	Bilateral spherophakia and *subluxation; bilateral* nystagmus and "poor vision"	"Short"	Brachydactyly and *stubby feet*

TABLE I—CONT'D

CASE AND SEX	AUTHOR	PARENTS	AGE OF ONSET OF EYE SYMPTOMS	EYES	STATURE	EXTREMITIES
14. J. V. Female	Arjona	Both fat and short; eyes and extremities normal	12 yr.	Bilateral microphakia with previous episode of severe bilateral eye pain O.S.: blind, T—12 mm. O.D.: almost blind (–50 diopters), T—25 mm.	Short, stocky build	Short extremities with brachydactyly
15. D. K. Male	Zabriskie and Reisman	Both short, with normal hands and eyes. First cousins	5 yr.	Bilateral spherophakia, subluxation, glaucoma, myopia, and lens extraction O.S.: retinal detachment and reattachment with diathermy, vision 20/200 O.D.: vision 20/70	Short, stocky, with broad chest; height at 9 yr., 44 inches	Short extremities with brachydactyly; cannot fully flex fingers to make fist
16. P. K. Male	Zabriskie and Reisman	Same as Case 15	5 yr.	Bilateral spherophakia, subluxation, and myopia; tensions ranged 20 to 60 mm.; vision –17 diopters	Short, stocky, with broad chest; height at 6 yr., 38 inches	Short extremities with brachydactyly; cannot fully flex fingers to make fist

TABLE II

CASE NUMBER*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	TOTAL
Eyes:																	
Spherophakia	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	16
Subluxation	×	–	–	–	×	×	–	–	×	×	–	–	×	–	×	×	8
Iridodonesis	–	×	×	×	–	×	–	–	–	–	–	–	–	–	–	–	4
Myopia	×	×	×	×	×	×	×	–	×	×	×	×	×	–	×	×	14
Glaucoma	×	×	NT	–	×	NT	×	×	–	–	×	–	–	×	×	×	9
Blindness	–	–	–	–	×	–	×	×	–	–	×	–	–	×	–	–	5
Lens extration	×	–	–	–	×	–	×	–	×	×	–	–	–	–	×	–	6
Age of onset of eye symptoms	8	–	–	–	13	7	9	9	–	6	–	–	9 mo.	12	5	5	Av. 7.5 yr.
Short stature	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	16
Brachydactyly	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	16
Heart	–	–	–	–	M	–	–	–	NM	NM	–	–	–	–	M	M	3
Intelligence:																	
Retarded			–	–		–		–		×	–	–	–				1
Average		×	–	–		–		–	×		–	–	–		×	×	4
Bright	×		–	–	×	–	×	–			–	–	–	×			4

× = Condition present.
- = *Not mentioned to be present.*
NT = Normal tension.
M = Murmur present.
NM = No murmur present.
*Case number corresponds to listing in Table I.

Five patients emerged blind, presumably as a result of the severe glaucoma, in spite of lens extractions in two of them. The age of onset of poor vision or eye symptoms is stated in ten cases, ranging from 9 months to 13 years, with an average of 7.5 years. Murmurs were described in three cases but no cardiac symptoms were noted. In nine cases some clinical impression of intelligence was mentioned and only one was felt to be "somewhat deficient."

DISCUSSION

Eyes.—Spherophakia, microphakia or "bullet lens" (Kugellinse) is, as its name implies, a thick spherical lens whose sagittal diameter is increased and whose equatorial diameter is decreased. Measurements of extracted lenses range from 4.5 to 4.9 mm. by 6.75 to 7.5 mm. for the sagittal and equatorial diameters, respectively.[1, 3, 14]

For clinical purposes the small lens can be demonstrated by fully dilating the pupil. Under these circumstances the periphery of the lens is visible in its entirety. Spherophakia by itself is rare. Gnad[15] in 1931 reported fifteen cases. There are probably only about twenty-five cases, not including those with Marchesani's syndrome, in the literature. Many are probably not recognized because such lenses subluxate and are then confused with dislocated lenses of other origin.[2]

Schmid[3] believes that spherophakia without changes in position of the lens is extremely rare and that there is always some degree of eccentricity. The zonular fibers supporting the lens may be stretched long and thin. These fibers, as well as the lens itself and the edge of the iris, may be seen to quiver tremulously. Quivering of the iris is referred to as iridodonesis and is associated with subluxation of the lens. The lens may be displaced downward, medially or laterally, and into the anterior or posterior chambers. With displacement the lens edge may be readily seen even through a small pupil.

As would be expected with a markedly convex lens there is a marked myopia. This is a pure lens myopia, inasmuch as the refractive correction after extraction is the same as for any other aphakic eye.[1]

As a result of the marked convexity of the lens and the displacement, there is increased pressure on the iris narrowing the angle of the anterior chamber, resulting in an increase in the tension and glaucoma.[1, 3] This was described in five of fifteen of Gnad's[15] cases. Miotics have been reported to aggravate the condition.[1, 14, 15]

In a family with hereditary glaucoma reported by Harshman,[12] six had dislocated lens. In these cases the lens were normal in shape, and onset of symptoms was in the fourth to the sixth decade. The glaucoma in these cases did not respond to the usual medical and surgical treatment but was permanently controlled only with lens extraction. Of the five cases with the Marchesani syndrome that underwent lens removal, two progressed to blindness while three apparently had good results. In our case D. K., there was a postoperative retinal detachment which reattached after diathermy treatment. Numerous other eye changes were observed inconstantly in one or more patients, including coloboma, chorioretinitis, leukoma, cataracts, and synechiae.

Stature.—The patients are short. The fifteen adults and late adolescents whose heights are listed range from

136 to 160 cm. with an average of 148 cm. (4 feet 10 inches). Their builds are stocky with broad chests and a tendency to heavy musculature. The extremities tend to be short. The heads have been described by several authors as "brachycephalic" with broad foreheads.

Hands.—The hands are strikingly small. The palms are thick, the fingers short and stubby, giving the impression of a thick, spadelike, or trident-shaped hand. In our two cases there was an inability to flex the fingers completely or to make a fist, although the children were adept in buttoning their clothes in an unconventional manner. X-rays of the hands showed symmetrical shortening and widening of the metacarpals and phalanges, and a marked retardation in carpal ossification. Marchesani made a similar observation in one of his patients (S. H.) in whom only three carpal centers were present at 8 years. In many cases the feet and toes have shared in the process and are described as small and stubby. Seeleman's patient did not need larger shoes after early childhood.

Heart.—In only one previous case (No. 5) was a cardiac murmur described. A systolic precordial murmur was heard, with a clinical impression of slight enlargement of the heart to the left and right. No further investigations were done. One of our two patients had evidence of an infundibular pulmonary stenosis, while the other had a probable intraventricular septal defect.

Etiology.—Marfan's syndrome, though quite rare, is well known. The patient is tall, tending to kyphosis and scoliosis of the spine. The extremities are long, with "spider fingers" (arachnodactyly). The musculature is hypoplastic, with a hyposthenic constitution. There is hypotonicity of the tendons and ligaments, which is evident as joint hyperextensibility and flat feet. In addition, a congenital ectopia lentis and congenital cardiac and vascular defects are often present. Weve,[8] in 1931, postulated a basic embryological mesodermal defect to explain the entire picture and coined the phrase "Dystrophia-mesodermalis congenita, Typus Marfans."

Marchesani and, later, Schmid commented on the striking contrast of their cases with those of Marfan. In Table III (adapted from Schmid[3]) it may be seen that the two syndromes are at opposite poles in many systemic respects and share similar lens defects.

Marchesani postulated that there was a single defect (dystrophia mesodermalis congenita), the two syndromes representing the hypoplastic

TABLE III

	MARFAN	MARCHESANI
Head	Dolichocephalic	Brachycephalic
Stature	Tall	Short
Bones	Long, delicate	Short
Hands	Arachnodactyly	Brachydactyly
Chest cage	Narrow	Broad
Musculature	Scanty	Heavy
Subcutaneous tissue	Scanty	Well developed
Tendons, ligaments	Loose, hyperextensible	Short, strong
Joints	Hyperextensible	Little motility
Lens	Ectopia lentis, microphakia	Ectopia lentis, microphakia
Other defects of mesodermal origin	Present (cardiac)	Present (cardiac ?)

(arachnodactylic) and hyperplastic (brachydactylic) variants. Schmid also accepted the mesodermal theory of Weve and preferred to use the term dolichomorphy (type Marfan) and brachymorphy (type Marchesani). The defect is presumed to originate in the first weeks of intrauterine life. Opinions differ as to the pathogenesis of the eye defect, inasmuch as the lens is ectodermal in origin. It is generally assumed that development of the lens is dependent upon development of the ciliary body which is largely of mesodermal origin. The fetal lens is spherical. Vogt[13] and Marchesani[1] postulated that, with a defect in the ciliary body, there is a reduction in the normal tension on the zonular fibers and lens. Thus an arrest in the ciliary development could lead to a congenital spherophakia. Schmid,[3] however, believes that growth of the microphakic lens is retarded owing to a defect in the perilenticular vascular tissue. Meyer and Holstein[2] note that the symptoms of spherophakia were not present until late childhood. They postulate that, inasmuch as the lens also tends to assume a spherical shape in maximum accommodation, hyperplasia of the ciliary body would have the same effect on the zonule and lens. Thus it might be conjectured that, paralleling the premature development and closure of the epiphyses, there is a precocious development of the mesodermal tissues of the eyeball, uncompensated for by similar ectodermal development, resulting in spherophakia and glaucoma.

In a series of 28 autopsied cases of Marfan's syndrome,[9] 89 per cent were found to have organic cardiovascular disease. Many patients had several organic defects. Thirty-nine per cent had aortic cystic necrosis, 54 per cent had aortic aneurysms, and 35 per cent suffered from aortic insufficiency. If Marfan's syndrome is a hypoplastic mesodermal defect, then the result of a defect in the cardiac elastic tissues would result in lesions of a "dilating" nature, i.e., insufficiency and aneurysm. If one further postulated the converse for the Marchesani or "hyperplastic" syndrome, one would expect cardiac lesions of a stenotic nature; our one case of pulmonary stenosis is compatible with this somewhat tenuous hypothesis.

Heredity.—There seems to be general agreement that the Marchesani syndrome represents an hereditary defect. There are apparently different forms of brachydactyly, possibly with different forms of inheritance. In the cases reported by McNutt,[10] there is an asymmetrical absence or reduction in the size of the various phalanges and metacarpals. He states that many, if not all, forms of human brachydactyly are the result of the same dominant autosomal gene with reduced penetrance and varying expression. Brachydactyly is also described as a part of the syndrome in pseudohypoparathyroidism and attributed to early fusion of the metacarpals.[11]

Arachnodactyly with ectopia lentis seems to follow a dominant pattern of inheritance, as does brachydactyly[1]; however, spherophakia is probably recessive.[1, 13] The appearance of incomplete syndromes (forme fruste), either spherophakia with normal extremities or brachydactyly with normal eyes, suggests that mild brachydactyly represents a heterozygous intermediate while severe spherophakia (with or without brachydactyly) represent the homozygous recessive form.[1, 3, 4, 5] The occurrence of consanguinity in several of the families further favors a homozygous recessive genotype.

The well-documented description of sixteen cases of the Marchesani syndrome over the past eighteen years establishes it as a definite entity. The full syndrome offers no diagnostic difficulties. Most of these cases will probably continue to be seen initially by the ophthalmologists because of the striking eye symptoms. The ophthalmologist who sees a child with high myopia and glaucoma will have to consider spherophakia as a possible cause. Similarly the pediatrician who sees a "brachymorphic" child will have to consider the Marchesani syndrome so that ophthalmologic investigations and supervision can be undertaken if the severe end results of untreated glaucoma are to be prevented.

On the basis of investigations up to the present, admittedly not extensive, there is little evidence to implicate a systemic (hormonal) or neurological defect. The symmetrical musculoskeletal involvement and bilateral eye changes suggest a congenital genetic defect.

The unifying mesodermal dystrophy theory, although speculative and adding little to our understanding, does provide a convenient framework for remembering the two contrasting syndromes, and might well be retained until further elucidating observations are made.

SUMMARY

1. The Marchesani syndrome, first described in 1939, consists of short stature, brachydactyly, and spherophakia, with associated myopia and glaucoma.

2. The literature and previous cases are reviewed and two new cases in male siblings are added to the fourteen already reported.

3. The striking contrast and possible relationship of the Marchesani syndrome to Marfan's syndrome are discussed.

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SICKLE CELL DISEASE WITH SALMONELLA OSTEOMYELITIS

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FOUR cases of Salmonella osteomyelitis are presented in children with sickle cell disease. Osteomyelitis due to Salmonella is uncommon, and its association with sickle cell disease in these and previously reported cases is considered to be more than coincidental.[1-5]

CASE REPORTS

CASE 1.—R. S. (C. H. 58462), a 7-month-old Negro male, known to be homozygous for sickle cell disease (S/S), was admitted to Children's Hospital with fever for twenty-four hours. Examination showed a febrile, irritable child with a slightly distended abdomen and enlarged liver. The hemoglobin was 7.7 Gm. per cent, the leukocyte count 6,100, with 90 per cent granulocytes. Five days after admission, swelling of the proximal phalanges was evident. Destructive changes in these areas and in the left acetabulum and right cuboid were noted radiographically. Material aspirated from the phalanges, as well as the blood cultures, yielded Salmonella sp. (Type Bredeney). The child was treated with oxytetracycline for six weeks with improvement. Two months later Salmonella sp. (Type Bredeney) was recovered from the stool during an episode of diarrhea.

CASE 2.—R. B. (C. H. 36164), a 4-year-old Negro boy with known sickle cell disease, was admitted to Children's Hospital with fever and a painful swollen right first toe. The hemoglobin was 7.2 Gm. per cent, the leukocyte count 41,000, with 75 per cent granulocytes. Salmonella sp. (Type Oranienburg) was recovered from the blood. A few days later focal destruction of the proximal diaphyses of the left fourth finger, the right first finger, and the left first metatarsal was evident by radiographs. Culture of the aspirated material yielded Salmonella sp. (Type Oranienburg). Uneventful recovery followed therapy with oxytetracycline, sulfisoxazole, and streptomycin. He was clinically well for one month, then developed bilateral lobar pneumonia and died. Salmonella was not cultured during this illness, and necropsy did not demonstrate osteomyelitis.

CASE 3.—S. W. (C. H. 116231), a 15-month-old Negro female, known to be homozygous for sickle cell disease (S/S), was admitted to Children's Hospital because her left foot had become increasingly painful during the preceding week. Examination disclosed splenomegaly and a fluctuant swelling of the dorsum of the left foot. The hemoglobin was 9.1 Gm. per cent, and the leukocyte count 13,500, with 52 per cent granulocytes. The abscess was drained of thick green pus from which *Salmonella typhimurium* was cultured. Two weeks later radiographic evidence of osteomyelitis of the left fifth metatarsal was present. The child was treated with tetracycline and sulfonamides and made an uneventful recovery.

CASE 4.—D. D. (U.C.L.A. 010-24-61), an 11-year-old Negro male, was admitted to the U.C.L.A. Hospital because of fever and pain in the left arm. The hemoglobin was 10.0 Gm. per cent, the leukocyte count 19,900, with 90

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per cent granulocytes. Many target and sickle cells were noted. Hemoglobin electrophoresis confirmed sickle cell-hemoglobin C disease (S/C). After a week of fever the left shoulder became painful, and radiographs were interpreted as showing epiphysitis of the head of the humerus. Salmonella sp. (Type Infantis) was recovered from the blood. Purulent material aspirated from the shoulder yielded the same organism. Uneventful recovery followed treatment with chloramphenicol, tetracycline, and streptomycin.

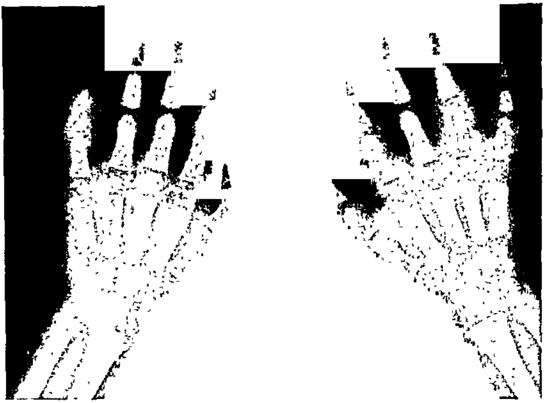

Fig. 1.—Radiograph showing osteomyelitis of the proximal phalanges in Case 1.

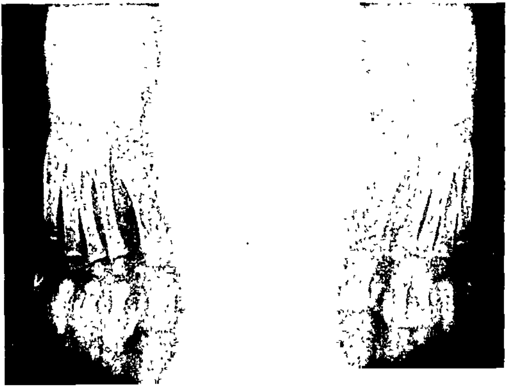

Fig. 2.—Radiograph showing osteomyelitis of the left first metatarsal in Case 2.

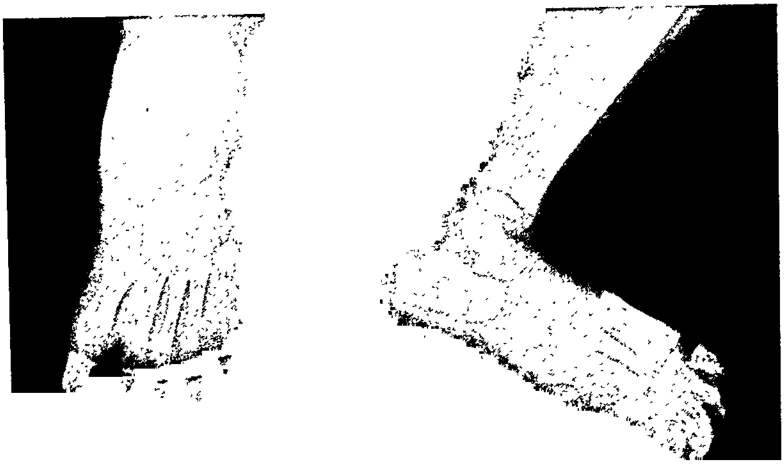

Fig. 3.—Radiograph showing osteomyelitis of the left fifth metatarsal in Case 3.

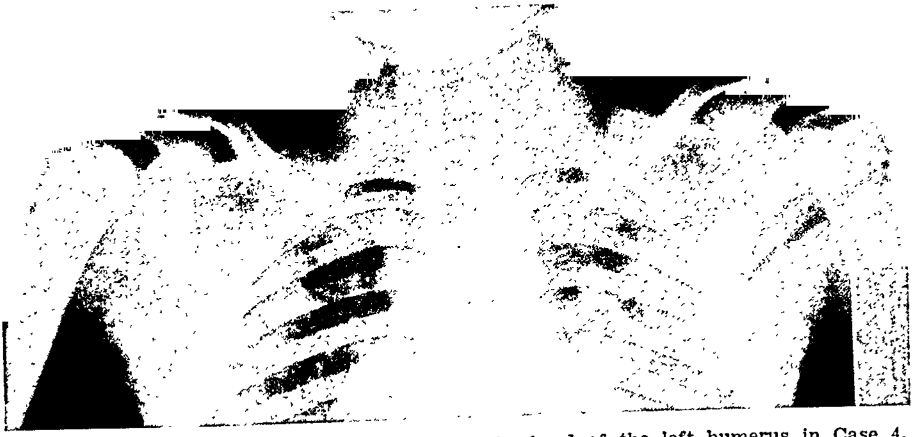

Fig. 4.—Radiograph showing osteomyelitis of the head of the left humerus in Case 4.

DISCUSSION

We have reported 4 new cases of osteomyelitis due to Salmonella in patients with sickle cell disease and summarized those previously reported in Tables I and II. In addition to the documented cases, Salmonella osteomyelitis has been reported in Negroes with incompletely studied anemia and recurrent arthralgia.[6, 7] One case of Salmonella osteomyelitis occurred in an Arab with undiagnosed hemolytic anemia, and another in a Jamaican with findings suggestive of sickle cell-hemoglobin C disease.[9] Harvey[10] presented 32 cases of *Salmonella choleraesuis* osteomyelitis. Twenty-seven of these patients were Negroes, but the coincidence of sickle cell disease was not noted. Hodges[11] commented on 5 cases of sickle cell disease with osteomyelitis due to *Salmonella paratyphi B.* Van Oye,[12] reviewing salmonellosis in the Belgian Congo, referred to fourteen salmonella cultures all isolated from osteomyelitis in Negroes with sickle cell disease.

TABLE I. SUMMARY OF PRESENT CASE REPORTS

AUTHOR	PATIENT	ORGANISM	SITE
Roberts and Hilburg[5]	7-month-old Negro male	Salmonella sp. (Type Bredeney)	Phalanges, tarsal
	15-month-old Negro female	*Salmonella typhimurium*	Metatarsal
	4-year-old Negro male	Salmonella sp. (Type Oranienburg)	Phalanges, metatarsal
	11-year-old Negro male (S/C)	Salmonella sp. (Type Infantis)	Humerus

TABLE II. CASE REPORTS OF SICKLE CELL DISEASE WITH SALMONELLA OSTEOMYELITIS

AUTHOR	PATIENT	ORGANISM	SITE
Diggs, Pulliam, and King,[24] (1937)	One	*S. paratyphi B*	"Arthritis"
Burch[25] (1949)	15-year-old Negro male	*S. paratyphi B*	Femur
Wigh and Thompson[14] (1950)	14-year-old Negro male	*S. paratyphi B*	Multiple
Mayer and Pohlidal[26] (1951)	27-year-old Negro male	Salmonella sp. (Type Montevideo)	Knee
Traisman and Champlin[27] (1951)	14-month-old Negro female	*S. typhimurium*	Multiple
Ehrenpreis and Schwinger[28] (1952)	Two	Salmonella sp.	Femur
Smith[1] (1953)	6-year-old Negro male	*S. choleraesuis*	Multiple
	9-year-old Negro female	*S. paratyphi B*	Multiple
	20-year-old Negro female	"Paracolon"	Humerus
Vandepitte et al.[2] (1953)	9-month-old Negro male	Salmonella sp. (Type Kisangani)	Metacarpal
	15-month-old Negro female	*S. typhimurium*	Multiple
	2½-year-old Negro female	*S. typhimurium* and others	Phalanges
	6-year-old Negro male	Salmonella sp. (Type Leopoldville)	Elbows
	11-year-old Negro male	*S. typhimurium*	Humerus, ribs
Choremis, Yannakos, and Bonta[3] (1955)	7-year-old Negro	*S. paratyphi*	Multiple
Ellenbogen, Raim, and Grossman[29] (1955)	27-month-old Negro	Salmonella sp. (Type Montevideo)	Humerus, radius
Goldenberg[15] (1955)	11-year-old Sicilian (sickle cell-thalassemia disease)	*S. enteritidis*	Multiple
Hughes and Carroll[4] (1957)	Negro male infant	*S. typhimurium*	Multiple
	3-year-old Negro male	*S. schottmuelleri*	Multiple
	3-year-old Negro male	Salmonella sp.	Multiple
	4-year-old Negro male	*S. schottmuelleri*	Humerus

Localization of Salmonella infection in bone is rare.[8, 13] Of 885 cases of osteomyelitis at the Los Angeles Children's Hospital, 3 were caused by Salmonella. These 3 children had sickle cell disease. Only 5 cases have been reported of sickle cell disease and osteomyelitis caused by *Micrococcus pyogenes* var. *aureus*.[2-4] In contrast, 26 cases of Salmonella osteomyelitis with sickle cell disease are presented in Tables I and II.

R. S. and R. B. of Cases 1 and 2 had dactylitis, S. W. of Case 3 presented with an abscess, and D. D. of Case 4 had a fever of unknown origin. The early radiographic changes did not distinguish osteomyelitis from uncomplicated sickle cell disease. Cortical fissuring, described by Wigh[14] as a radiographic sign of osteomyelitis in sickle cell disease, was present in later examinations. The difficulty in differentiating sickle cell crisis with bone involvement from bone infection is apparent. Osteomyelitis due to Salmonella must be considered whenever the course of a patient with sickle cell disease suggests bone infection.

Case 4, commencing as aseptic necrosis of the head of the humerus, is the first report of sickle cell-hemoglobin C disease (S/C) complicated by Salmonella osteomyelitis. Goldenberg[15] noted a case of Salmonella osteomyelitis in sickle cell-thalassemia disease. Smith and Conley[16] stated that aseptic necrosis of the head of the humerus is common in sickle cell-hemoglobin C disease (S/C), but unknown in homozygous sickle cell disease (S/S).

Salmonella osteomyelitis in sickle cell disease may be contrasted to Salmonella osteomyelitis in general. Trauma frequently predisposes to Salmonella osteomyelitis.[9, 17] No trauma is evident in cases of Salmonella osteomyelitis with sickle cell disease. Most cases of Salmonella osteomyelitis are due to *Salmonella paratyphi B* and *Salmonella choleraesuis*.[17] Perhaps 50 per cent of infections with *Salmonella choleraesuis* localize in bones.[18] On the other hand, osteomyelitis due to Salmonella in association with sickle disease is not caused by a predominant species. Multiple foci are found in 15 per cent of cases of Salmonella osteomyelitis[8] and, in contrast, in 65 per cent of those complicated by sickle cell disease (Table II).

Salmonella infections are usually manifest as enteritis or less commonly as hematogenous spread to bone or other organs.[10, 17, 19] Surgery of the intestinal tract increases the apparent incidence of Salmonella infections.[20] Similarly, injury to the intestine from sickle cell thrombosis may allow easy passage of Salmonella into the blood stream with activation of infection. It has been reported that Salmonella linger in bone marrow long after other sites are sterile.[21, 22] Vandepitte[2] believes that local bone changes allow proliferation of previously dormant medullary foci of Salmonella. The changes in bone resulting from thrombosis, infarction, and fibrosis found in sickle cell disease have been discussed by Caffey[23] and others.[14, 24] Transient Salmonella bacteremia may thus localize infection in bone injured by sickle cell disease.

SUMMARY

A more than coincidental association between Salmonella osteomyelitis and sickle cell disease is suggested by our 4 cases and a review of the cases previously reported.

We postulate that the bone changes caused by sicklemia may result in Salmonella osteomyelitis from previously dormant medullary organisms or from transient bacteremia.

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ACUTE LEUKEMIA AND MONGOLISM

Report of Two Cases

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TWO recent reports independently have emphasized anew the possible biological significance of the simultaneous occurrence of acute leukemia and mongolism in children. Krivit and Good[1] published data on five cases in which acute leukemia and mongolism were found together. Of these five cases, four were seen within a one-year period. The authors calculated that the chance occurrence of a single leukemia-mongolism combination was 1/10,000,000, "an experience to be anticipated in Minnesota once in 50 to 100 years." In a survey of the clinical records of 255 children with the diagnosis of mongolism, Merrit and Harris[2] found four instances in which acute leukemia developed. They concluded that among these children the incidence of leukemia was "much higher than in the general population."

The clinical infrequency of these combinations and their extremely high statistical significance indicate the desirability of documentation and reporting of all such cases. In a three-year period between July, 1954, and June, 1957, the bone marrow diagnosis of acute leukemia was made in 56 patients 14 years of age and under at The University of Texas M. D. Anderson Hospital and Tumor Institute. Two of these children had definite stigmata of mongolism. The case histories of these two patients are presented.

CASE REPORTS

CASE 1.*—A 22-month-old white girl was admitted on Dec. 14, 1955, with a history of loss of appetite and decreased activity beginning 2½ months previously. Possibility of an upper respiratory infection was suspected and the child was initially treated with antibiotics. Leg pain developed and the child stopped playing and walking. The patient was admitted to a nearby hospital, where anemia was noted. On the basis of a subsequent bone marrow biopsy, diagnosis of acute lymphocytic leukemia was made on Nov. 23, 1955. The child received two transfusions and four days of 6-mercaptopurine therapy before transfer to this hospital.

Past History.—This was the first child of an 18-year-old mother and a 22-year-old father. There was no consanguinity between the parents. Neither parent had received radiation therapy. Pregnancy was uncomplicated. The patient weighed 7 pounds 2 ounces at birth. General physical and mental development was retarded, but otherwise no significant complaints were noted in the past medical history.

Physical Examination.—The patient was a pale-appearing, white girl with mongoloid facies. Several petechiae were noted on the legs. Fontanels were open. Generalized adenopathy was present. The eyes were

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*Referred by Dr. G. Daeschner, Houston, Texas.

slanted and epicanthic folds were present. Dentition consisted of four upper and four lower teeth. The spleen was palpable 4 cm. and liver 5 cm. below the costal margins. Both little fingers were curved. Joints were hyperextensible and musculature was generally flabby. Head circumference was 40.3 cm., head length 13.2 cm., head width 11.4 cm. Body weight was 9.4 Kg., body length 80 cm.

Hematologic Data.—The blood findings were as follows: hemoglobin 12.4 Gm., red blood cells 4,120,000, platelets 30,000, reticulocytes 0.6 per cent, white blood cells, 2,000; differential: segmented neutrophils 6 per cent, stabs 4 per cent, normal lymphocytes eighty-six per cent, monocytes one per cent, basophils one per cent, atypical lymphocytes two per cent; blood type O, Rh positive. Bone marrow study showed almost complete replacement of normal elements by lymphoblasts and immature lymphocytes. Very few granulocytes or normoblasts were noted. No megakaryocytes were seen. Diagnosis of acute lymphocytic leukemia was made.

Laboratory Data.—Urinalysis showed no abnormal findings. Kline exclusion test for syphilis gave negative results. Total serum protein was 6.5 Gm., with 4.8/1.7 A/G ratio. Examination of the stools revealed no ova or parasites.

X-ray Studies.—Definite leukemic destruction of bone was noted in both tibias, both femurs, both humeri, and pelvis. Over-all skeleton appeared deossified. A probable destructive process also involved the basisphenoid. Middle phalanx of each little finger was hypoplastic. Hypoplasia of the nasal bone was also apparent. Lung fields showed some exaggeration of the vascular markings, but no frank infiltration or consolidation was noted. Skeletal age was assessed at 12 months.

Clinical Course.—On 6-mercaptopurine, transfusions and symptomatic therapy, a fairly satisfactory clinical remission and a partial hematologic remission were maintained for approximately one month. Subsequent therapy with adrenal steroids and A methopterin did not significantly alter the course of the disease. The clinical picture was complicated by the occurrence, in succession, of mouth ulcers, thrush, diarrheic episodes, and urinary tract infection. Thrombocytopenia, bleeding tendency, and anemia persisted. Terminally, there was an abrupt rise in white count with cells consisting predominantly of blast cells. The child died on May 7, 1956.

Autopsy.—This 24-month-old white girl with mongolism measured 32 inches in length and weighed 24 pounds. Lymph nodes in cervical, axillary, and inguinal regions were slightly enlarged. Eyes showed epicanthus and pale conjunctivae. Mouth revealed irregular dentition. Abdomen was protuberant with prominent superficial veins. Skin showed marked pallor with pinhead-sized petechiae scattered over the abdomen and anterior chest wall. The little fingers were incurved. The lymph nodes of the mediastinum, mesentery, and retroperitoneal groups were enlarged. The liver weighed 410 grams; its cut surface bulged and the acinar marks were obscured. A tumor nodule, round in shape, measuring 3 by 2 cm. was located in the right lobe of the liver near the right triangular ligament. The nodule showed firm consistency and was of grayish-pink color. The spleen weighed 45 grams. The cut surface was dark purple and firm in consistency. The right kidney weighed 48 grams, left kidney 46 grams. Cut surface showed firm grayish yellow pattern. Design of medullary substance was clear. Several foci of hemorrhagic infiltration were located in the wall of the stomach and small intestines. Heart showed no anomalies. Microscopically, a tremendous amount of leukemic infiltration was noted in the liver. This infiltration appeared to be primarily around the portal triads. Leukemic infiltration was also noted in the kidneys, lungs, and beneath the endocardium of the heart.

CASE 2.*—A 16-month-old white girl was admitted on May 22, 1957, with a history of pallor first noted two months before admission. The child had become less active and more irritable. "Anemia" was found and iron therapy was instituted by the family physician. Four weeks before admission, the child had a questionable convulsive episode. Intermittent fever developed and a week later the child stopped walking. Appetite became poor. Over the week preceding admission, she developed generalized edema.

Past History.—This is the fifth child of a 37-year-old mother and the ninth child of a 56-year-old father, both of whom have been married before. There is no consanguinity between the parents. Neither parent has received any radiation therapy. The mother had vaginal "spotting" beginning about the third month and recurring occasionally throughout the pregnancy. About the third month the mother also had a "virus infection" with high fever and cough, but no rash. The child weighed 6 pounds at birth; cyanosis was prominent and resuscitation was somewhat difficult. There is a history of jaundice in the baby which was noted at 6 weeks of age and lasted about one month. Motor and mental development has been noticeably retarded "two months or so behind the other children."

Physical Examination.—The patient was an acutely ill, irritable child with characteristic mongoloid facies. Marked pallor and generalized edema were present. No jaundice, no bruises, and no petechiae were noted. Lymph nodes measuring 0.25 to 0.5 cm. in size were palpable in the cervical, axillary, and inguinal areas. Palpebral fissures were obliquely slanted. Epicanthic folds were prominent. The eyes appeared small and were set widely apart across a depressed nasal bridge. The head was brachycephalic with somewhat flattened occiput. A Grade II systolic heart murmur was heard over the entire precordium. The area of cardiac dullness was enlarged to percussion. The liver extended 7.5 cm. and the spleen 7 cm. below the costal margins. The fingers were short and stubby. All the joints were hyperextensible and the muscles felt flabby.

Anthropometric Data.—Body length was 73 cm. and body weight 9.1 Kg. Head circumference measured 42.8 cm., head length 14.4 cm., and head width 11.8 cm. Skeletal age was assessed at seven months.

Dermatoglyphics showed the following:

	Left	*Right*
Digital patterns	5 4 3 2 1 W U U U U	1 2 3 4 5 U U U U U
Hallucal pattern	arch tibial	arch tibial
Axial triradius (height)	2.6/5.1 (51%)	1.8/4.4 (41%)
Third interdigital configuration	D	D
Palmar main line index	11	11

Hematologic Data.—The blood findings were as follows: hemoglobin 6.3 Gm., platelets 20,000, white blood cells, 13,300, reticulocytes 7.0 per cent; differential: 28 per cent segmented neutrophils, 8 per cent stab neutrophils, 22 per cent normal lymphocytes, 10 per cent monocytes, 1 per cent myelocytes, 31 per cent blasts. Marked hypochromia and anisocytosis were noted. Few target cells and many macrocytic red cells were seen. There were 673 nucleated red cells per 100 white cells in the peripheral smear. Blood type was A, Rh positive. Bone marrow differential was as follows: granulocytic series 6 per cent, red cell series 32 per cent, normal lymphocytes 10 per cent, blasts and leukemic cells 52 per cent. The hematologist felt that the extremely hyperplastic marrow showed a very unusual pattern. This was characterized by hyperplasia of immature reticuloendothelial elements, of myeloblasts, and of immature erythrocytic elements. The erythrocytic elements were of abnormal morphology, although primarily normoblastic in type. No megakaryocytes were seen. The diagnosis of acute myeloblastic leukemia was made although the possibility of "erythroleukemia" was also considered.

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*Referred by Dr. C. Nau, San Antonio, Texas.

Laboratory Data.—Urinalysis showed no abnormal findings. Blood urea nitrogen was 23 mg. per cent, uric acid 5.72 mg. per cent. Serological test for syphilis gave a negative reaction.

X-ray Studies.—Lung fields showed no abnormalities. Heart appeared generally enlarged. Bone survey revealed no abnormalities. No anomalies of the facial bones or of the bones of the hand were seen.

Clinical Course.—Treatment with 6-mercaptopurine-DON combination was started. The clinical picture stabilized rather promptly. At the time of last examination (June 8, 1957) the child was in fair clinical remission and was beginning to show hematologic response to therapy.

COMMENTS

The pathogenesis of acute leukemia in children is unknown. While it is recognized that ionizing radiation is leukemogenic,[3] radiation as the probable etiologic factor can be established only in the very exceptional instance of acute leukemia among children.[4, 5] Experimentally, other agents such as carcinogenic hydrocarbons and estrogenic hormones induce leukemia in certain animals. Genetic strain, hormones, age, and other factors influence the incidence of leukemia in these animals.[6] Animal data, however, cannot be used directly to explain human leukemia.[7]

The cause of mongolism, too, is obscure. It has been postulated that teratogenic factors acting on the organism between the sixth and ninth weeks of fetal life produce the various stigmata of mongolism.[8] This hypothesis is based on experimental observations that specific developmental defects follow when deleterious influences act at specific developmental stages. Evidence for this "time specificity" of teratogenic effects has been reviewed by Wilson.[9] As a corollary it is presumed that the presence of certain developmental defects indicates the action of a teratogenic agent at a particular developmental period. The synchronism of associated anatomic malformations in mongolism do suggest a common teratogenic zone on the developmental time scale.[8]

The coincident occurrence of the two conditions in numbers far exceeding the statistically expected frequency arouses speculation that the deleterious stress leading to developmental anomalies of mongolism also trigger the maldevelopment of the blood dyscrasia. Suggestions along this line have been made in the earlier sporadic case reports.[10, 11] Such a contention receives strong support from tabulations of reported data (Table I). In 6 out of 20 instances the leukemia occurring concomitantly with mongolism is of the congenital type. The rarity of congenital leukemia is emphasized by the study of Dalgaard and Kass[12] who, in their extensive survey of the literature from 1888 to 1955, accumulated data on 52 cases of "congenital leukemia" from 44 published reports, including their own. Of these, only 34 cases satisfactorily fulfill the diagnostic criteria set up by the authors. The probability of the chance occurrence, therefore, of even a single case of was also noted in the kidneys, lungs, and beneath the endocardium of the heart.

CASE 2.*—A 16-month-old white girl was admitted on May 22, 1957, with a history of pallor first noted two months before admission. The child had become less active and more irritable. "Anemia" was found and iron therapy was instituted by the family physician. Four weeks before admission, the child had a questionable convulsive episode. Intermittent fever developed and a week later the child stopped walking. Appetite became poor. Over the week preceding admission, she developed generalized edema.

Past History.—This is the fifth child of a 37-year-old mother and the ninth child of a 56-year-old father, both of whom have been married before. There is no consanguinity between the parents. Neither parent has received any radiation therapy. The mother had vaginal "spotting" beginning about the third month and recurring occasionally throughout the pregnancy. About the third month the mother also had a "virus infection" with high fever and cough, but no rash. The child weighed 6 pounds at birth; cyanosis was prominent and resuscitation was somewhat difficult. There is a history of jaundice in the baby which was noted at 6 weeks of age and lasted about one month. Motor and mental development has been noticeably retarded "two months or so behind the other children."

Physical Examination.—The patient was an acutely ill, irritable child with characteristic mongoloid facies. Marked pallor and generalized edema were present. No jaundice, no bruises, and no petechiae were noted. Lymph nodes measuring 0.25 to 0.5 cm. in size were palpable in the cervical, axillary, and inguinal areas. Palpebral fissures were obliquely slanted. Epicanthic folds were prominent. The eyes appeared small and were set widely apart across a depressed nasal bridge. The head was brachycephalic with somewhat flattened occiput. A Grade II systolic heart murmur was heard over the entire precordium. The area of cardiac dullness was enlarged to percussion. The liver extended 7.5 cm. and the spleen 7 cm. below the costal margins. The fingers were short and stubby. All the joints were hyperextensible and the muscles felt flabby.

Anthropometric Data.—Body length was 73 cm. and body weight 9.1 Kg. Head circumference measured 42.8 cm., head length 14.4 cm., and head width 11.8 cm. Skeletal age was assessed at seven months.

Dermatoglyphics showed the following:

	Left	*Right*
Digital patterns	5 4 3 2 1 W U U U U	1 2 3 4 5 U U U U U
Hallucal pattern	arch tibial	arch tibial
Axial triradius (height)	2.6/5.1 (51%)	1.8/4.4 (41%)
Third interdigital configuration	D	D
Palmar main line index	11	11

Hematologic Data.—The blood findings were as follows: hemoglobin 6.3 Gm., platelets 20,000, white blood cells, 13,300, reticulocytes 7.0 per cent; differential: 28 per cent segmented neutrophils, 8 per cent stab neutrophils, 22 per cent normal lymphocytes, 10 per cent monocytes, 1 per cent myelocytes, 31 per cent blasts. Marked hypochromia and anisocytosis were noted. Few target cells and many macrocytic red cells were seen. There were 673 nucleated red cells per 100 white cells in the peripheral smear. Blood type was A, Rh positive. Bone marrow differential was as follows: granulocytic series 6 per cent, red cell series 32 per cent, normal lymphocytes 10 per cent, blasts and leukemic cells 52 per cent. The hematologist felt that the extremely hyperplastic marrow showed a very unusual pattern. This was characterized by hyperplasia of immature reticuloendothelial

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*Referred by Dr. C. Nau, San Antonio, Texas.

SUMMARY

Clinical information is reported on two children in whom acute leukemia and mongolism occurred simultaneously.

ADDENDUM

A second report by Krivit and Good (A. M. A. J. Dis. Child. 94: 289, 1957) further emphasizes the possible significance of the simultaneous occurrence of acute leukemia and mongolism.

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GARGOYLISM

(HURLER'S SYNDROME; LIPOCHONDRODYSTROPHY; DYSOSTOSIS MULTIPLEX)

REPORT OF TWO CASES IN NEGROID CHILDREN

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GARGOYLISM is a rare hereditary disorder characterized by bizarre skeletal deformities and the presence of an abnormal storage substance which may be present in the brain, cornea, liver, spleen, lymph nodes, and other organs of the body. The first report of the skeletal deformities was made by Hunter[1] in the *Proceedings of the Royal Society of Medicine,* in 1917. The first description of the complete syndrome, however, including evidence of abnormal storage, was made in 1919 by Hurler[2] in Munich.

The disease is world-wide in distribution and occurs in all races. McKusick[3] however, commented on the rarity of reported cases in the Negro. Hubeny and Delano[4] reported a case in a male Negro child in 1941 and Townsend-Coles[5] reported 3 cases of the disease in Northern Sudanese natives.

Recently, two brothers with the disease were admitted to this hospital. Because of the rarity of reported cases in the Negro, these cases are presented.

CASE REPORTS

CASE 1.—A. McD., a 3½-year-old male, was admitted on June 26, 1956, for diagnostic studies. He was born Nov. 27, 1952. The mother's health was good during the pregnancy. Delivery was spontaneous and without complications. Weight at birth was 3.54 kilograms. The father was 22 years old and the mother was 26 years old at the time of his birth. There are two siblings—a girl, 2 years of age, in good health; and a boy, 15 months of age, who is retarded and anemic (Case 2). The mother was in her fourth pregnancy at the time of the patient's admission, and while he was hospitalized gave birth to a premature male who appeared normal.

At 9 months of age, the patient sat alone; he walked at 17 months. The mother states that, at 6 months of age, he began to say monosyllabic words to indicate his needs. This, however, ceased at 10 months of age, after an attack of pneumonia, and he had not talked since. His appetite has always been good. He has received multiple vitamin supplement in his diet since the age of 2½ weeks. His weight at 1 year was 11.36 kilograms.

He had experienced frequent illnesses since he was 7 months old. At that time, he was hospitalized for a bilateral inguinal herniorrhaphy. Two weeks following operation, he developed pneumonia. At 1½ years of age he developed "asthma." Since the age of 10 months, he has had frequent respiratory infections. Six months prior to admission, the parents were told that he had an enlarged heart and liver.

According to the mother, the patient had presented a problem in discipline at home. He was disobedient and showed no regard for authority. At night, he often awoke screaming at imaginary objects.

From the Department of Pediatrics of Howard University College of Medicine and the Pediatric Service of Freedmen's Hospital.

Physical Findings.—The patient was a well-developed, well-nourished male with a large body structure (Figs. 1 and 2). Anthropometric measurements are presented in Table I. Mild oxycephaly was present. The sclerae were dark and mottled. The bridge of the nose was flattened. A thick white nasal discharge was present. The teeth were small with wide spaces between them. The tonsils were slightly enlarged. The neck was short so that the head appeared to rest directly on the shoulders. Mild cardiomegaly was present but no cardiac murmur or arrhythmia was elicited.

The abdomen was markedly enlarged. Bilateral inguinal herniorrhaphy scars were present. The liver could be percussed 5 cm. below the right costal margin and the spleen was palpable. The shoulders could not be fully abducted. The knees and elbows were partially flexed and could not be fully extended. The hands and feet were broad and short. The fingers were held in flexion and could not be fully extended (Fig. 3). When standing, the patient often swayed from side to side and assumed a crouching position. There was a tendency to walk on the toes.

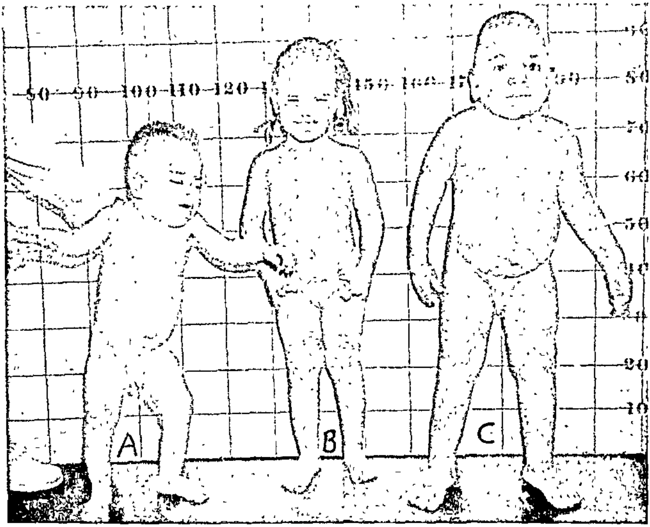

Fig. 1.—Photograph of the patients and their normal sister. Case 1 is illustrated in *C* and Case 2 is depicted in *A*. Note the short appearance of the necks. Mild oxycephaly is demonstrated in the boy on the right (Case 1).

Laboratory Studies.—The white blood cell count was 5,200 per cubic millimeter, hemoglobin 12.3 Gm. per 100 ml., hematocrit 40 per cent and erythrocyte sedimentation rate 10 mm. in one hour. A differential count showed 38 per cent leukocytes, 29 per cent large lymphocytes, 12 per cent small lymphocytes, 19 per cent monocytes, 3 per cent eosinophils, and 4 per cent basophils. A bone marrow specimen was essentially normal. The serological test for syphilis was negative. Urinalysis was within normal limits. Other blood examinations are presented in Table II.

TABLE I. SUMMARY OF ANTHROPOMETRIC MEASUREMENTS

PATIENT	AGE (MONTHS)	HEIGHT (CM.)	WEIGHT (KILOGRAMS)	SPAN (CM.)	UPPER MEAS. (CM.)	LOWER MEAS. (CM.)	RATIO UPPER/LOWER	HEAD CIRCUM. (CM.)	CHEST CIRCUM. (CM.)	ABDOMEN CIRCUM. (CM.)
Case 1	42	95.0	22.3	95.0	51.25	43.75	1.17	53.13	61.5	70.0
Case 2	15	71.85	9.9	75.0	42.47	29.37	1.45	45.0	50.0	51.25

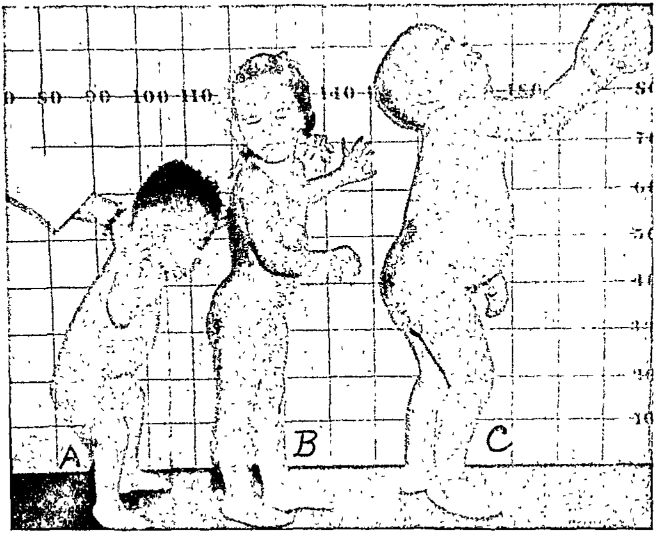

Fig. 2.—Lateral view of the two patients and their normal sister, showing the enlarged abdomens and partial flexion of the knees. Case 1 is illustrated in *C* and Case 2 in *A*.

Slit-lamp examination of the eyes revealed no inclusion bodies or opacities. The electrocardiogram and electroencephalogram were normal.

Psychogalvanic skin resistance audiometry indicated normal end organ function on the right and some impairment on the left. He did not respond normally to environmental sounds. Ear, nose, and throat examination showed no gross abnormality that might cause the hearing or speech

Table II. Blood Chemistry Determinations in Case 1

Nonprotein nitrogen	40 mg. per 100 ml.	
Glucose	83 mg. per 100 ml.	
Total protein	6.29 Gm. per 100 ml.	
Albumin	4.30 Gm. per 100 ml.	Ratio 2.14
Globulin	1.90 Gm. per 100 ml.	
Calcium	8.85 mg. per 100 ml.	
Inorganic phosphorus	4.66 mg. per 100 ml.	
Sodium	141.0 mEq. per liter	
Potassium	4.8 mEq. per liter	
Protein-bound iodine	4.9 µg per 100 ml.	
Icterus index	3.0 units	
Cholesterol, total	239 mg. per 100 ml.	
Cholesterol, esters	112 mg. per 100 ml.	
Cephalin flocculation	2 plus in 24 hours; 4 plus in 48 hours	
Glutamic oxaloacetic transaminase	24 units	
Plasma protein (paper electrophoresis)	Albumin	58.6%
	Alpha globulin	11.0%
	Beta globulin	17.1%
	Gamma globulin	13.4%

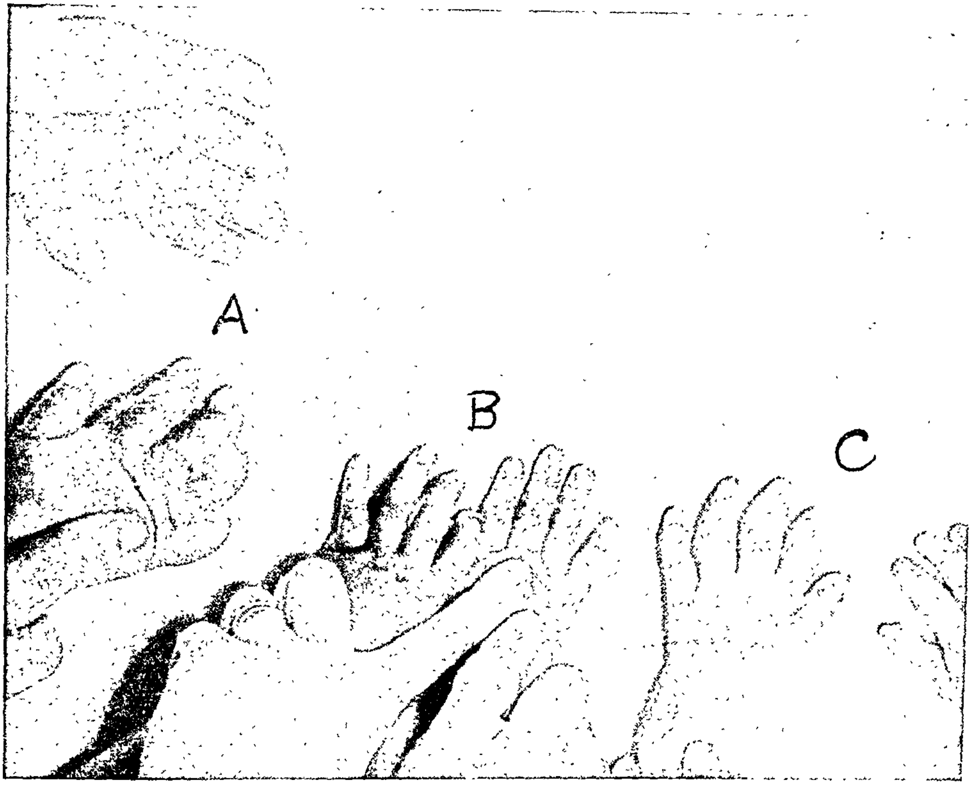

Fig. 3.—Note the flexion of the terminal phalanges in Case 1 (*A*) and Case 2 (*C*), compared with normal sibling (*B*).

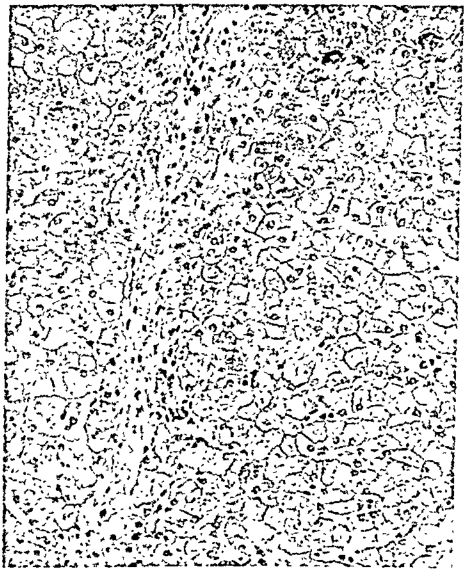

Fig. 4.—Photomicrograph of section of the liver showing vacuolation of the cytoplasm and increased fibrosis in the portal triads.

defect. Psychometric studies indicated that the patient's mental age was about 1 year.

A section of liver was obtained for biopsy. Microscopic examination showed distention of the cytoplasm of the hepatic plate cells by a finely vacuolated material which in many areas was dissolved out by formalin (Fig. 4). The vacuolated material gave negative results to fat stain (sudan IV). There was increased fibrosis within the portal triads. Masson's stain showed an increased amount of collagen in the portal triads and these sometimes extended to adjacent portal triads producing pseudolobules.

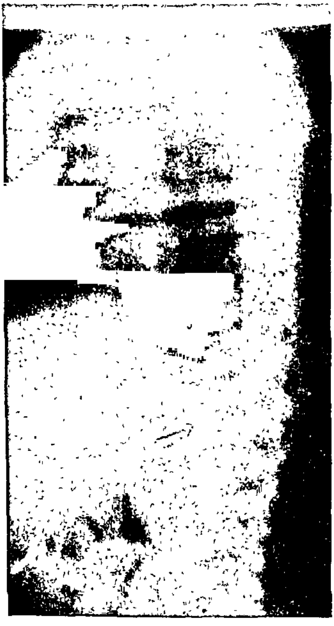

Fig. 5.—Lateral view of roentgenogram of the spine (Case 1). Arrow indicates hypoplastic twelfth dorsal vertebra.

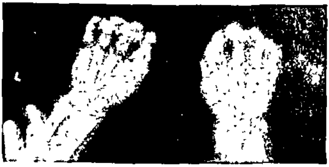

Fig. 6.—Roentgenogram of the hands (Case 1). The metacarpal bones are irregular in shape and tend to be pointed at their proximal ends.

Roentgenologic Findings.—Examination of the chest disclosed a ribbon-like appearance of the ribs, which varied in size and shape. The cardiac silhouette was enlarged and there was mild congestion of the lungs. The twelfth dorsal vertebra showed a slight loss of substance from its anterior superior aspect which was associated with a slight degree of sclerosis (Fig. 5). There was evidence of sclerosis involving each humerus. Each radius and ulna appeared osteoporotic. Typically, the metacarpal bones were broad and pointed at the proximal ends (Fig. 6). No roentgenographic evidence of rickets was present.

CASE 2.—M. McD., a 15-month-old male, was admitted on Sept. 5, 1956. He is the brother of the patient presented in Case 1 and was brought to the hospital for study. The patient was born in the home and weighed 2.0 kilograms at birth. The mother was "anemic" during this pregnancy and took multiple vitamins and a special diet. Shortly after birth, he developed diarrhea and an upper respiratory infection and was hospitalized for 15 days. At 2 months of age, he was operated upon for an incarcerated inguinal hernia. He also received treatment periodically for bronchiolitis, anemia, malnutrition, and otitis media.

The patient sat at 13 months. He could not stand alone, walk, or say any words at 15 months. His appetite was good but he would accept only strained foods. According to information supplied by the mother, multiple-vitamin supplement was not added to the diet until the child was 1 year of age.

Physical Findings.—The patient was a fairly well-developed, well-nourished 15-month-old male, who appeared alert and observant. His weight on admission was 9.9 kilograms. Pertinent body measurements are presented in Table I. The forehead was prominent with protruding temporal bones. The bridge of the nose was flat and crusts were present in the nares. The eyes were essentially normal. The neck was short and thick (Figs. 1 and 2). The chest was symmetrical with some flaring of the lower rib margins. Harsh breath sounds were heard throughout the lung fields. The point of maximal impulse of the heart was located in the fifth intercostal space to the left of the midclavicular line. No murmur was heard. The abdomen protruded. A right inguinal herniorrhaphy scar was noted. The spleen was enlarged 7 cm. below the left costal margin. He tended to hold his hands in a claw-like position (Fig. 3). The feet were broad. The patient's arms could not be fully extended at the elbow and there was limited abduction at the shoulder joints. There was partial flexion of the knees (Fig. 2). Both testes were in the scrotal sac. Phimosis was present. A fine lanugo-like fuzz was present over the body.

Laboratory Studies.—The white blood cell count was 5,600 per cubic millimeter, hemoglobin 9.3 Gm. per 100 ml., hematocrit 33 per cent, and erythrocyte sedimentation rate 35 mm. in one hour. The serological test for syphilis was negative. Other blood studies are presented in Table III. Urinalysis showed no abnormalities. Slit-lamp examination of the cornea failed to disclose opacities or inclusion bodies. The electroencephalogram and electrocardiogram were normal.

Roentgenologic Findings.—The patient's second, third, fourth, and fifth metacarpal bones were somewhat irregular and somewhat pointed at the proximal ends. The chest showed ribbon-like ribs with variation in size and shape. The cardiac silhouette was enlarged. There was no roentgenographic evidence of rickets.

DISCUSSION

The occurrence of the disease in siblings, especially brothers, is not an uncommon finding. The appearance of the disorder in children of apparently normal parents suggests that the latter may be carriers of a single recessive gene. Washington[12] pointed out that, for carriers of such a gene to transmit the disease, they must marry other carriers. This accounts for the rarity of the disease in the general population except when there is parental consanguinity. By this mode of inheritance males and females are equally affected. In order to explain the preponderance of affected males in published series, a sex-linked form of inheritance has also been proposed for some cases.

The two boys described in this report are representative of gargoylism in childhood. Few, if any, affected individuals show all the reported characteristic signs of the disease[6] (Table IV). Some of the cases are atypical and wide variations (forme fruste) have been reported.[7] The differential diagnosis of any given case, therefore, would depend largely on the predominating signs and symptoms.

Gargoylism is often mistaken for cretinism since the stunted growth, the retarded mental development, the shortness of the extremities, and the appearance of the hand form a syndrome which resembles cretinism on superficial examination. The abnormalities of the bones seen in the roentgenogram, enlargement of the spleen or liver, and cloudiness of the cornea make the diagnosis of gargoylism possible.

Morquio's disease is similar, with dwarfism, atypical facies, and various

TABLE III. BLOOD CHEMISTRY DETERMINATIONS IN CASE 2

Nonprotein nitrogen	30 mg. per 100 ml.	
Glucose	107 mg. per 100 ml.	
CO_2	21 mEq. per liter	
Chlorides	105 mEq. per liter	
Total protein	6.41 Gm. per 100 ml.	
Albumin	4.66 Gm. per 100 ml.	Ratio 2.66
Globulin	1.75 Gm. per 100 ml.	
Calcium	9.70 mg. per 100 ml.	
Inorganic phosphorus	4.66 mg. per 100 ml.	
Prothrombin time	100% of control	
Icterus index	9.8 units	
Total bilirubin	0.394 mg. per 100 ml.	
Direct van den Bergh reaction	0.093 mg. per 100 ml.	
Cholesterol, total	132 mg. per 100 ml.	
Alkaline phosphatase	11.16 Bodansky units per 100 ml.	
Cephalin flocculation	1 plus in 24 hours; 2 plus in 48 hours	
Glutamic oxaloacetic transaminase	30 units	
Plasma protein (paper electrophoresis)	Albumin	50.0%
	Alpha globulin	12.0%
	Beta globulin	20.0%
	Gamma globulin	18.0%

TABLE IV. SUMMARY OF REPORTED FINDINGS IN GARGOYLISM

General:	Grotesque appearance and asymmetrical dwarfism, mental retardation
Local:	
Head	Large and prominent, dull facies
Nose	Flattened bridge, chronic "rhinitis"
Eyes	Hypertelorism, clouding of cornea
Ears	Impaired hearing
Mouth	Small, widely spaced, malformed teeth, mouth breathing, enlarged tongue, enlarged adenoids
Neck	Very short
Thorax	Flaring of lower rib cage, funnel chest, cardiomegaly, systolic murmurs
Spine	Kyphosis, gibbus
Abdomen	Protuberant, hepatosplenomegaly, diastasis recti, umbilical and inguinal hernia
Extremities	Broad hands, stubby fingers, flexion contracture of fingers, limited joint extensibility
X-ray:	
Skull	Long, shallow sella turcica with anterior "pocketing," separation of sutures, platybasia, marked deformities of facial bones
Clavicles	Thickened
Ribs	Broad, saber shaped, or spatulate
Vertebrae	Wedge-shaped deformity of body with anterior beaking
Extremities	Short, thick radii and ulnae with distorted distal epiphyses, broad and stubby metacarpals with coarse trabeculations, proximal ends pointed, short, misshapen phalanges

bone deformities; however, mental deficiency, enlargement of the liver, and clouding of the cornea are absent.[8] The bone deformities of rickets may externally resemble gargoylism. Both diseases may involve the bones of the skull, thorax, spine, pelvis, and extremities. The history, chemical determinations on the blood, and roentgenograms of the bones aid in distinguishing them.

Reduced mobility of the joints such as is seen in gargoylism is a characteristic of arthrogryposis multiplex congenita.[9] The subcutaneous tissues are likely to feel thick, doughy, and gelatinous. Inguinal hernia occurs, as well as congenital anomalies such as hypospadias, cleft palate, cryptorchidism, micrognathia, and mental deficiency. However, clouding of the cornea and evidence of abnormal storage are not present.

Some of the other conditions to be differentiated from gargoylism are juvenile amaurotic idiocy, congenital syphilis, and craniofacial dysostosis of Crouzon.

Bone lesions have been present in all reported cases. In about 75 per cent of the reported cases there has been evidence of corneal clouding.[10] Jackson[6] concluded that the diagnosis rests essentially on the presence of coexistent characteristic osseous lesions along with evidence of an abnormal storage substance such as corneal clouding, mental defect, or hepatosplenomegaly.

Victims of this disease appear to be particularly susceptible to acute respiratory infections, and bronchopneumonia is a chief cause of death. The exact chemical nature of the storage substance is not clear. It has been variously described as being lipid or glycolipid, complex polysaccharide (glycogen), or glycoprotein.[11] There was a slight increase in the beta globulin fraction of the serum proteins in our cases. There is no effective treatment for the syndrome.

SUMMARY

Because of the rarity of reported cases of gargoylism in the Negro, the cases of two brothers with this disease are presented. The pathological findings in the liver of one of the patients are also reported. A discussion of the differential diagnosis is given.

Appreciation is expressed to Dr. Allan E. Walker, Jr., Director of the Hearing and Speech Clinic, Children's Hospital, who provided facilities for obtaining the psychogalvanic skin resistance audiometry; to Dr. Frank B. Johnson and Dr. S. Rosen (Armed *Forces Institute of Pathology*) and Dr. Morris Weinberger (Department of Pathology, Howard University College of Medicine) who gave assistance in the preparation of histopathological illustrations; and to Dr. John A. Washington, who saw the patients in consultation.

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COARCTATION OF THE ABDOMINAL AORTA

A CASE SUCCESSFULLY TREATED SURGICALLY

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ALTHOUGH coarctation of the abdominal aorta is considered a very rare condition, more cases have been reported in the past 8 years than in the 102 years following the first case described by Quain in 1847. Undoubtedly, this is due to our increasing knowledge and interest in cardiovascular disease, as well as to better diagnostic aids such as aortography. With such continued interest this condition will probably be diagnosed clinically with increasing frequency. Ten of the 18 cases reported in the literature were not surgically treated. Nine of these 10 cases were reviewed by Inmon and Pollock,[1] and 8 of these constitute autopsy reports. Two patients[1, 2] had aortography only. Six of the 10 patients died because of the complications of the coarctation of the abdominal aorta.

The 8 remaining patients have had various surgical procedures. Glenn and associates[3] removed the spleen and used the splenic artery to bypass the coarcted aorta, with a good result. In two cases reviewed by the previous authors[1, 3] a lumbar sympathectomy was performed with slight improvement. Albanese and Baila[4] reported a patient in whom a homologous graft was inserted below the renal arteries, who died postoperatively of anuria and encephalopathy. Two patients reviewed by Inmon and Pollock[1] had nephrectomies without benefit and died. Another patient reported by the same authors had a laparotomy only. Beattie and associates[5] successfully used a graft to replace the aortic coarctation at the level of the diaphragm.

Our patient was treated surgically; however, the coarctation was corrected during a second major operation after a previous thoracotomy had been performed. It is the purpose of this report to record the first case of coarctation of the abdominal aorta in the region of the celiac axis treated successfully in which a homologous aortic graft was used with an excellent result. In addition we wish to point out two errors which were made clinically and radiologically prior to the definitive surgical procedure. In view of the diagnostic importance now placed upon angiography[6] in the diagnosis of congenital cardiovascular anomalies, we must re-emphasize the value of a thorough clinical examination of the patient and proper correlation of the clinical with the radiographic findings in making a final diagnosis previous to surgical therapy.

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CASE REPORT

S. L. O., an 11-year-old white girl, was first seen in the Pediatric Clinic of the U. S. Naval Hospital, Corona, California, on March 9, 1956. The history revealed that a heart murmur was noted in February, 1956, by the family doctor during an examination for an upper respiratory infection. The patient had no symptoms referable to the cardiovascular system. When hypertension was found in association with the heart murmur, the child was referred to a cardiologist. In March, 1956, examination by the cardiologist revealed a blood pressure of 180/120 in both arms, diminished femoral pulsations, and inability to obtain a blood pressure in either leg. The examination otherwise was reported as normal except for a systolic murmur, Grade III in intensity, along the left sternal border, which also was heard in the left posterior chest. A_2 was greater than P_2. Laboratory tests on that examination revealed: hemoglobin 14.4 Gm.; red blood cells, 4.77 million; white blood cells, 7,600; differential count of 54 neutrophils and 46 lymphocytes; sedimentation rate of 7 mm. in one hour. X-rays of the chest and fluoroscopy revealed rounding of the left ventricular shadow suggestive of early hypertrophy. The aortic knob was prominent. The electrocardiogram revealed S-T segment depression in V_5 and V_6. The corrected Q-T was 0.26. A diagnosis of coarctation of the aorta was made by the cardiologist.

A review of systems revealed that the patient began having frontal headaches at 7 years of age. These occurred about three or four times each year and were associated with nervousness and occasional nausea. They had not increased in frequency or severity. There was no past history of edema, intermittent claudication, dyspnea, or easy fatigability. There had been no abdominal pains or infections of unusual nature in the gastrointestinal tract. There had been no visual complaints.

The past history showed that the child had grown and developed normally and had had the usual contagious diseases without complications. She had had tonsillitis with ear infections frequently until the age of 5 years when a tonsillectomy and adenoidectomy were performed.

Family history revealed that the father had occasional migraine headaches. There was no history of hypertension. The mother and father were in good health as was an 8-year-old sibling who was found to be normal on examination.

Physical condition was normal except for the same cardiovascular findings noted above. Funduscopic examination was normal.

The patient was referred to the cardiac clinic of St. Mary's Hospital in Long Beach, California, where cardiac studies were performed on April 10, 1956. The angiocardiogram performed was interpreted as showing an area of narrowing at the distal aspect of the arch of the aorta which was consistent with the usual type of coarctation of the thoracic aorta. Operation was advised but deferred until the end of the school term.

First Hospital Admission.—The patient was admitted July 9 and discharged July 23, 1956.

Interval history revealed that the patient had been well since the initial examination except for occasional minor frontal headaches and easy fatigability at times. General appearance revealed a well-developed but thin white female. Weight was 75 pounds, temperature was 99.6° F., pulse was 120, and blood pressure was 170/120 in both arms and 0/0 in both legs. The examination was entirely normal except for a Grade I (I-IV) systolic murmur heard over the precordium as noted previously.

Laboratory findings were as follows: Hemoglobin was 13.6 grams. Bleeding time was 1 minute 30 seconds, and coagulation time was 3 minutes 30 seconds. A urinalysis was normal with a specific gravity of 1.028. A chest x-ray revealed a normal chest although there was questionable broadening of the supracardiac silhouette. An electrocardiogram showed S-T segment depression in chest Leads V_5 and V_6 which was interpreted as early evidence of left ventricular hypertrophy.

On July 11 the patient was given a general anesthetic and placed in the lateral decubitus position with the left side uppermost. A left parascapular incision was made. A moderate amount of increased collateral circulation was noted in the extracostal tissues. The fourth interspace was entered. The mediastinal pleura was incised over the aorta, and the upper portion of the descending aorta and the aortic arch freed from surrounding tissue. No definite coarctation could be seen. The fibrous portion of the ductus arteriosus was ligated and divided. No lumen was found. On palpation of the lower thoracic aorta a thrill was felt at the aortic hiatus of the diaphragm and it was noted that the intercostal vessels in the lower thorax were much larger than those visualized above. Therefore, an oblique extension of the previous incision was made and was carried down over the eighth interspace. The lower portion of the thoracic aorta and the upper portion of the abdominal aorta were exposed. About 2 cm. caudal to the aortic hiatus the aorta became almost solid. A thrill could be felt over this firm area. Since the exposure was not very good and the operation had been prolonged, the procedure was terminated.

The patient made a rapid recovery, and on July 20 a retrograde aortogram was performed using Urokon (70 per cent). Serial films were made. The films showed a coarctation approximately 3 cm. in length extending from the level of the first lumbar vertebra to about 2 to 3 cm. above the origins of the renal arteries (Fig. 1). Considerable collateral circulation was noted between the lower intercostal and lumbar arteries. Both kidneys were well visualized and showed prompt dye excretion and normal configuration. The patient tolerated the procedure well.

On July 23, the day of discharge, a thorough examination (by A. M. M.) revealed a systolic sonorous murmur along the left sternal border which varied with pulse and respiratory rates as well as position. This was also heard in the neck. A second faint harsh systolic murmur could be heard in the sixth intercostal space. A third systolic murmur Grade II (I-IV) was noted over the epigastrium. No thrill was palpated nor were the femoral pulses palpable. A_2 was snapping in character and louder than P_2. Arterial pulsations were felt posteriorly, only with careful scrutiny, in the tenth and eleventh intercostal spaces. Blood pressure was 180/120 lying down and 180/130 in the sitting position with a large cuff on the right arm.

Second Hospital Admission.—The patient was admitted July 30 and discharged Aug. 8, 1956.

Interval history revealed that the patient had been well. General appearance revealed a well-developed but thin, blonde girl, 11 years of age. Physical findings were: temperature, 99.4° F. orally; blood pressure, 190/160; height, 58 inches; weight, 62½ pounds; pulse, 128; and respiration, 24. Examination was normal except for the following cardiovascular findings in addition to those noted on July 23. The thorax posteriorly revealed several areas of pulsation in T_{10} and T_{11} intercostal spaces which on auscultation revealed an inconstant, high-pitched bruit. On the left side of the T_{10} spinous process a continuous murmur could be heard. On the right side of the T_{10} thoracic spine a systolic bruit was heard. This was low pitched and was Grade I (I-IV). The two cardiac systolic murmurs as noted previously were unchanged. The third murmur which was previously heard in the left epigastrium was now continuous, Grade I (I-IV), and was harsh in quality. The loudest component was found to follow the second heart sound. There was no thrill.

A repeat blood count, urinalysis, and hematocrit were normal. Six urinalyses were normal and showed good concentration.

The patient was started on penicillin preoperatively. On August 1 she was given a general anesthetic, placed in an ice bath for one half hour, and her temperature was slowly lowered from 99° F. (rectally) to 86.1° F.

umbilicus. The abdominal aorta was exposed retroperitoneally. There was a very slight pulsation felt in the abdominal aorta below the renal vessels which appeared normal and were found to come off in the usual manner (Fig. 2). About 1 to 1.5 cm. above the renal vessels the abdominal aorta was found to be very firm and a systolic thrill could be felt. The diaphragm was next incised in the direction of the ninth rib and the incision carried medially posteriorly to the aortic hiatus. The thoracic aorta was mobilized for a distance of 7 cm. above the aortic hiatus and two umbilical tapes were placed about it.

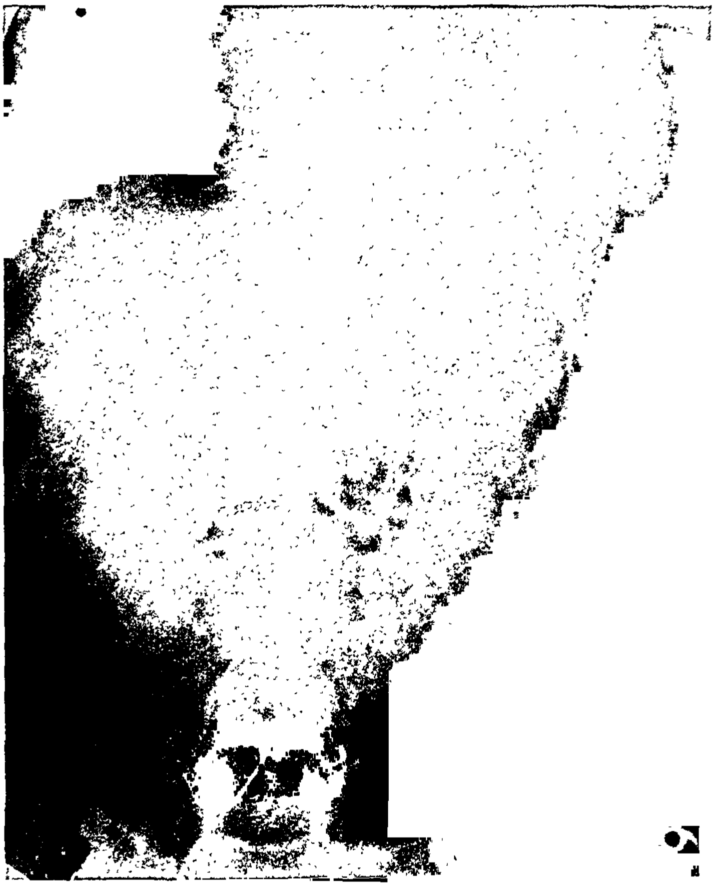

Fig. 1.—Film made during retrograde aortagram via right femoral artery showing coarcted segment just above renal arteries and collateral circulation. Note dilated tortuous lower intercostals which anastomose inferiorly with lumbar arteries. Pyelogram is a result of previous injection of Diodrast.

The operative procedure was as follows: The patient was placed in a semilateral position with the left side uppermost. An incision was made through the ninth intercostal space and carried down over the anterior abdominal wall to a level 3 cm. below the

The diameter of the thoracic aorta measured about 3 cm. and had a very forceful pulsation. Two cm. below the aortic hiatus the aorta, which could now be palpated more easily, was found to be practically solid with no pulsation. The systolic thrill could be felt at the distal portion of this solid area. The coarcted portion of the aorta measured approximately 2 to 3 cm. in length and had the same caliber (3 cm.) as the upper portion of the thoracic aorta. Therefore, the narrowing of the aorta was apparently intraluminal since the caliber of the vessel from the external appearance did not appear to be narrowed. There was an abundance of nerve and scar tissue about this solid portion. An attempt was made to dissect out this area, but due to the presence of this dense adherent tissue it was felt that it was too hazardous to warrant such a dissection. The aorta distal to the coarctation measured 1 cm. in diameter and had a normal-appearing wall. A Satinsky clamp was placed on the lower portion of the thoracic aorta just above the aortic hiatus and a linear incision 2.5 cm. in length was made. The proximal end of the homologous thoracic aortic graft (previously

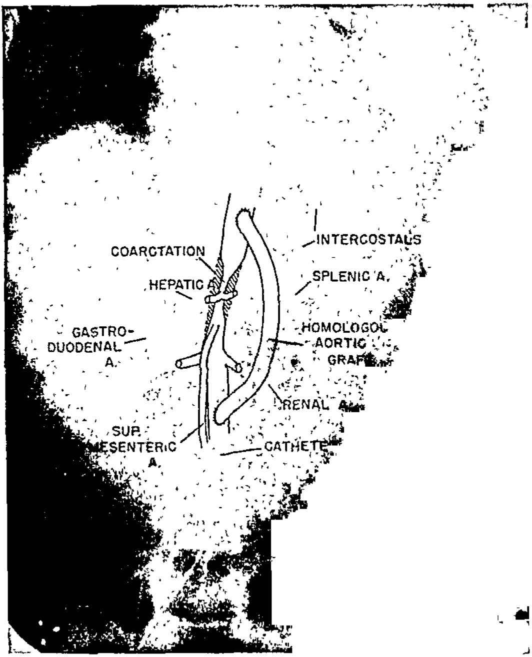

Fig. 2.—Composite roentgenogram of the abdominal and lower thoracic aorta with superimposed diagram to show the extent of the abdominal coarctation. The operative procedure performed, that is, the insertion of an homologous aortic graft about the stricture, is diagrammatically demonstrated.

lyophilized and soaked in saline for restoration) was then sutured end-to-side to the aorta with 5-0 arterial silk sutures. After anastomosis of this portion of the graft, which measured 2.5 cm. in diameter and 13 cm. long, the distal end was sutured to the abdominal aorta end-to-side 1 cm. beyond the renal arteries. Blood was noted to course through the graft and good pulsations were felt in the abdominal aorta (Fig. 2) following the release of all the clamps. Following closure of the wound the femoral pulses were found to be very strong on the left and fair on the right.

The patient tolerated the procedure very well. She lost about 3,500 c.c. of blood, which was replaced by 4,000 c.c. The operative procedure was without incident except at one point when the blood pressure was momentarily unobtainable as the distal anastomosis of the aortic shunt was being made. At the onset of the operative procedure the blood pressure was 200/120. This gradually fell and was 145/90 at the end of the 5-hour surgical procedure.

The postoperative course was relatively uneventful. The blood pressure varied between 112 to 170 systolic and 80 to 120 diastolic. The sonorous heart murmur was still heard over the precordium. Neither the previous harsh systolic murmur noted along the left sternal border nor the extracardiac murmurs noted in the epigastrium and in the posterior thoracic areas could be heard. The femoral pulsations as well as the posterior tibial artery pulsations were easily palpated. On August 7, the day before discharge, a sonorous Grade I (I-IV) murmur was heard in the midepigastric area on deep pressure with the stethoscope. Examination was entirely normal otherwise, and the blood pressure was 120/98.

Outpatient Course.—On Aug. 15, 1956, the patient was well except for some pain along the incision. She noted that her feet felt warmer than usual. Examination revealed pulse 112; blood pressure 135/110 left arm, and 130/122 right arm; weight 66 pounds; temperature 98° F. orally. Other findings were normal except for a faint systolic sonorous murmur heard in the epigastric area. Femoral, posterior tibal and dorsalis pedis arterial pulsations were present bilaterally. One week later the patient had gained weight and looked better. Examination revealed weight 70 pounds; temperature 99° F.; pulse 88; blood pressure 118/94 left arm, 116/96 right arm; 126/92 left leg and 128/96 right leg. The patient was advised to continue limited activity. Two weeks later the patient was well and the blood pressure was 108/96.

On Nov. 7, 1956, the patient was well. She had been active, with only limited restriction such as vigorous exercise. Weight was 75 pounds and blood pressure 105/75. The complete examination was normal except for a faint systolic bruit in the mid-epigastric area. The femoral and posterior tibial pulsations were normal. Three months later the patient continued to do well. Weight was 79½ pounds; height 59½ inches; temperature 99.2° F.; blood pressure right arm 110/65, left arm 115/75, right popliteal 90-70-40, left popliteal 125/80 with a large cuff; pulse 100. Physical examination was entirely normal except for an inconstant, faint sonorous murmur heard along the left sternal border. Good aortic pulsations were noted in the midabdomen and a faint systolic sonorous bruit was heard above the umbilicus. The femoral and posterior tibial pulsations were palpable, but the right posterior tibial pulsations seemed to be decreased. Both dorsalis pedis pulsations were barely felt. Laboratory data revealed a normal urinalysis and blood count, a sedimentation rate of 27 (Wintrobe), and a hematocrit of 45. X-rays of the chest showed regeneration of the removed portions of the ribs of the left lower hemithorax. There was a minimal residual pleural scarring. The lungs were clear. The cardiac silhouette was normal except for a slight prominence in the region of the pulmonary artery. An x-ray of the abdomen was normal.

On May 8, 1957, the patient was quite well and had been on full activity during the previous two months. Menstruation had started and was normal. Examination was unchanged except for the absence of the cardiac murmur. The blood pressure was 110/70 in the arms, 120/80 in the left leg, and 95/75 in the right leg. Weight was 85 pounds. X-rays of the chest and abdomen were unchanged. A urinalysis, blood urea nitrogen, blood count and sedimentation rate were normal.

COMMENT

From this case and a review of the literature it is apparent that hypertension is universal in all cases of coarctation of the aorta. This finding is perhaps the most significant of all in directing a differential diagnosis toward the possibility of coarctation. If hypertension is found on routine examination, it should follow that the popliteal blood pressure be ascertained next in order to rule out disparity between the two locations. Having been prompted by the blood pressure findings, a careful examination for pulsations and bruits over the entire chest and abdomen should always be made. In the reported case the presence of the murmur heard over the epigastrium and the pulsations and bruit heard over the lower posterior chest should have led to a diagnosis of coarctation of the abdominal aorta had they been critically evaluated prior to surgery. Thus a second major surgical procedure probably would have been avoided.

Once the diagnosis is suspected, the only accurate adjunctive modality is radiographic study by means of angiography or aortography, which, when properly performed and evaluated, will localize and show the degree and extent of the stenosis and the amount of collateralization in addition to eliminating other congenital vascular anomalies. Although this is not entirely without danger the morbidity figures are extremely low and certainly the information gained justifies the examination. When intravenous injection is employed, the results are not always satisfactory due to the considerable dilution of the opaque material by the time it reaches the aorta. This factor may have been the major cause of the error made in the interpretation of the angiocardiogram in our patient. The most satisfactory method is catheterization of the radial artery with placement of the catheter tip in the middle segment of the ascending aorta. In our case, or any case in which abdominal coarctation is suspected, it is felt that a retrograde approach by catheterization of a superficial femoral artery is the procedure of choice. This was accomplished without difficulty and the results were satisfactory (Fig. 1).

This case is of unusual interest because the narrowing of the aorta was above the renal arteries and involved the celiac axis. In most of the reported cases of coarctation of the abdominal aorta the constriction has been below or at the level of the renal arteries. The ideal method for correcting a stenosis of the thoracic or abdominal aorta is to excise the deformity and reanastomose the ends of the aorta, or to replace the stenotic area with a homologous graft if the narrowing is located where this is feasible. We chose to bypass the entire defect because of its unusual location. If a replacement graft had been inserted, it would have been most difficult to anastomose the branches of the celiac axis to the graft since these vessels were of such small caliber that the likelihood of such anastomoses remaining patent would indeed have been small.

Most authors state that the ideal age for operation in any case of coarctation whether it be abdominal or thoracic is from 5 to 15 years. This agrees with other recent reports[7, 8] which show the mortality rate to be lowest (6.8 per cent) between 4 and 15 years of age. Satisfactory reduction in the hypertension which occurred in our case, as it does in 90 per cent of these patients[9] following surgery, is more likely to result in the younger age group.

SUMMARY AND CONCLUSIONS

This is the first case of coarctation of the abdominal aorta limited to the area of the celiac axis which has been treated successfully using an aortic homograft as a shunt about the constricted area. A brief review of the literature is given. The importance of a thorough physical examination and correlation with the roentgenographic study prior to surgery has been reemphasized. Surgical correction of such lesions is the only satisfactory method of treatment.

We are indebted to Herbert Movius, M.D., Long Beach, Calif., for his surgical assistance.

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SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN INFANCY

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INTRODUCTION

THE problem of patent ductus arteriosus in infancy was not fully appreciated until its importance was emphasized by Ziegler[1] in 1952. He pointed out that twenty of Abbott's[2] series of ninety-two autopsied cases were in infants. Similarly, Wilson and Lubschey[3] reported autopsies on sixteen patients with uncomplicated patent ductus arteriosus. Death resulted in fourteen of these before 1 year of age. Several other reports[4] have revealed that patent ductus arteriosus in infancy may result in cardiac enlargement, congestive heart failure, and death. Keith and Forsyth[5] demonstrated the presence of a patent ductus arteriosus by aortography in six infants with cardiac enlargement and/or congestive failure. Ziegler[1] added seventeen under the age of 3 to this list and commented on the value of the operation. Closure was successful in fifteen, while one died preoperatively and one during induction anesthesia.

In 1954, Lyon and Kaplan[6] reported five symptomatic infants from their clinic with uncomplicated patent ductus arteriosus. In four of these, successful closure of the ductus arteriosus was carried out.

These reports emphasized the importance of patent ductus arteriosus in infancy and showed that operation at this age was followed by rapid recovery. All reported the difficulty of diagnosis but pointed out the value of the occurrence of the usual signs. In several cases special procedures, such as cardiac catheterization, angiocardiography, and retrograde aortography, were required to establish the diagnosis.

In the past four years we have observed ten infants who were operated prior to the age of 2½ years. The findings in these ten patients are herein reported, further emphasizing the importance of detecting this lesion in infancy.

SUMMARY OF SIGNIFICANT FINDINGS

The significant clinical and laboratory findings are given in Table I. The youngest patient at the time of operation was 9 months old. Nine of the ten were below the "average weight range" for their chronological age, and the "normal" sized infant gained weight noticeably after operation (Fig. 1). Eight of the remaining nine have been followed from a few months to four years. The weights of seven plotted against their ages show a definite tendency toward gain after operation (Fig. 2). The tenth

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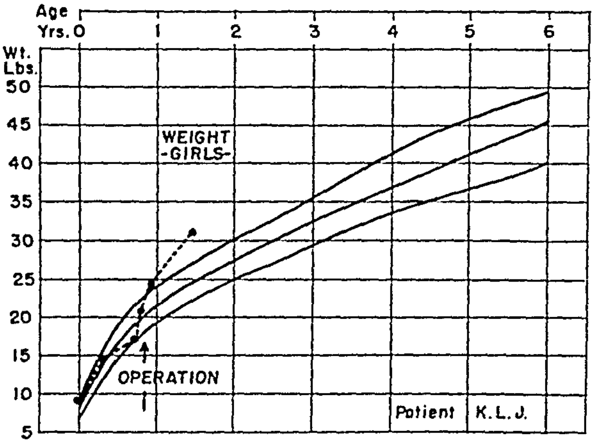


Fig. 1.—Weight chart on patient K. L. J., illustrating the increase in weight following surgery.

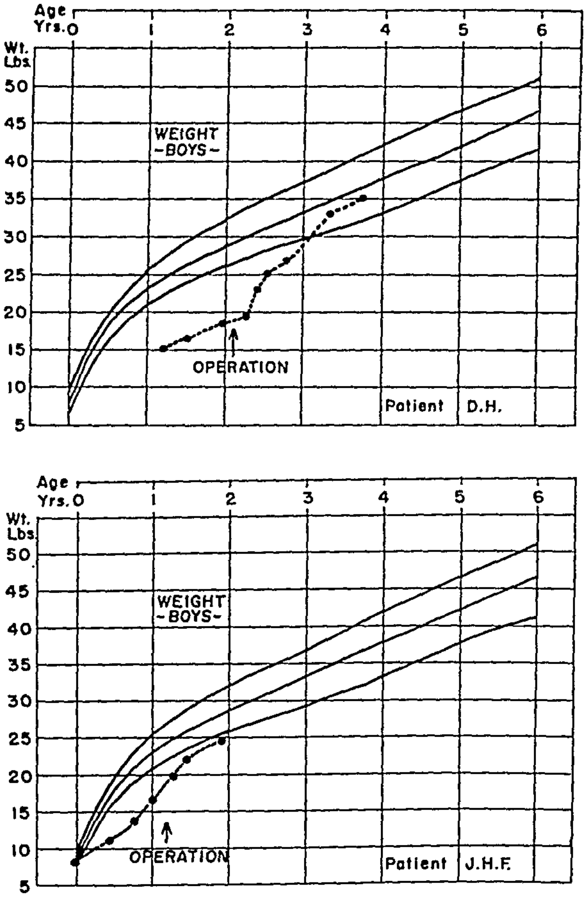


Fig. 2.—Weight charts on two patients illustrating the weight response following surgery.

patient has not been followed long enough for indication of a trend.

Patient J. T. (Fig. 3) gained weight during medical management; operation could probably have been safely delayed until she was older. Since she had had one bout of congestive failure with a compatible x-ray picture, it was felt that surgery was indicated. Of the ten, seven had had one or more bouts of congestive failure, requiring digitalization and continued maintenance therapy until completion of surgery.

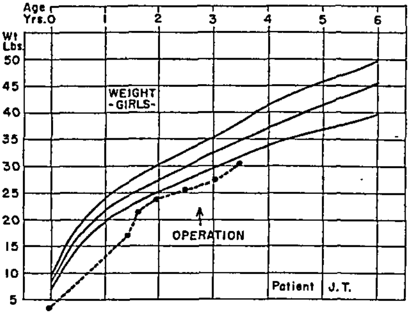
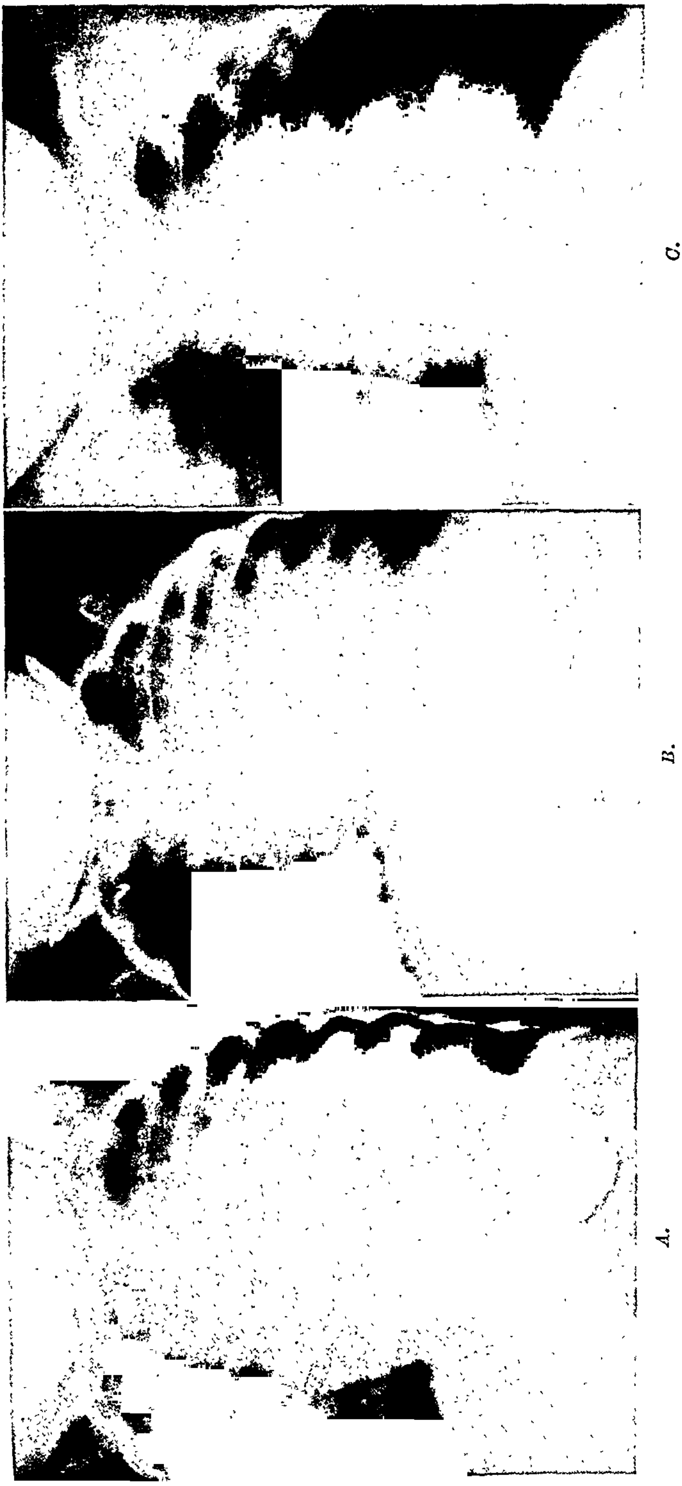


Fig. 3.—Weight response of patient J. T.

The other physical findings were variable. Four of the ten had diastolic as well as systolic murmurs. These were of the "classical" ductus murmur type. The youngest patient with a "classical" murmur was 6 months old. The other murmurs were not described as continuous until after the first year of life. Five had loud, harsh systolic murmurs heard all over the precordium. Two were loudest in the second and third left intercostal spaces, two in the third, and one in the third and fourth. Six had a palpable systolic thrill, and patient K. L. J. developed a thrill when 9 months old. The thrill in each instance was located at the point of maximum intensity of the murmur.

The blood pressure was diagnostically helpful in five patients. Four had a normal pressure. One electrocardiogram was read as normal, one showed right ventricular hypertrophy, five left ventricular hypertrophy, and three combined hypertrophy.

At cardiac fluoroscopy nine of the ten (Fig. 4) were found to have cardiomegaly of some degree. The other patient's heart was at the "upper limits of normal." Seven had evidence on opacification of the esophagus of left atrial enlargement. The pulmonary vascularity was increased in six (Fig. 5), at the upper limits of normal in two, and normal in two. Postoperative radiological examination revealed a tendency for the cardiomegaly to decrease (Fig. 4). This occurred more as a result of the growth of the chest as there was little or no change in cardiac size. The pulmonary vascularity also became normal



A. B. C.

Fig. 4.—Serial teleoroentgenograms on patient M. S., illustrating the usual changes seen (*A*) at time of operation, (*B*) one month postoperatively, and (*C*) approximately seven months postoperatively.

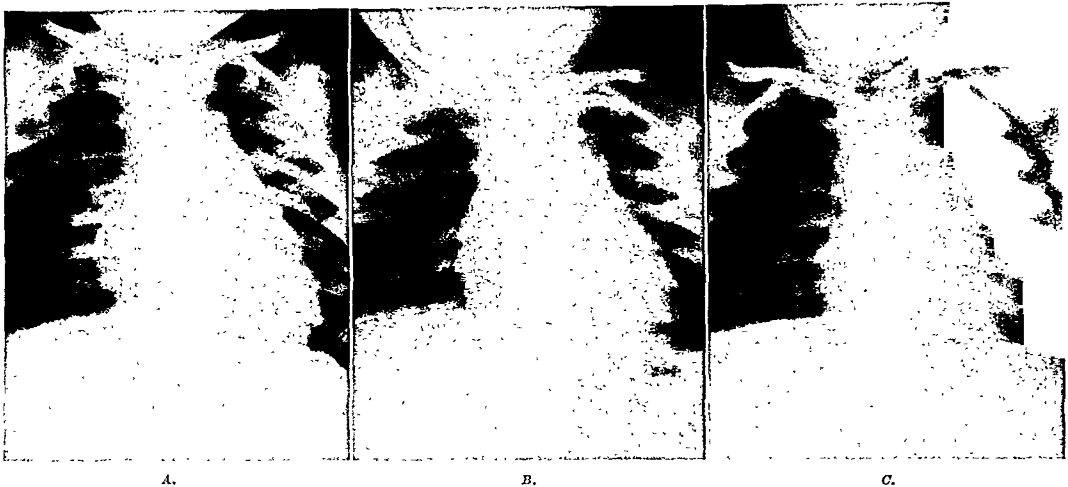


Fig. 5.—Serial teleoroentgenograms on patient J. A. D., illustrating particularly the change in vascularity of the lung fields (*A*) at time of operation, (*B*) one month postoperatively, and (*C*) six months postoperatively.

TABLE I. SUMMARY

PATIENT	SEX	AGE IN MONTHS		CLINICAL FINDINGS					EKG
		FIRST OBSERVED	OPERATED UPON	GROWTH	MURMURS		THRILL	BLOOD PRESSURE (MM. HG.)	
					SYS.	DIA.			
D. R.	F	6	24	R.	+	+	+	120/64	R. V. H.
M. S.	F	2	9	R.	+	0	+		L. V. H.
D. K. H.	M	15	25	R.	+	+	0	134/80	L. V. H.
J. T.	F	5	30	R.	+	0 - +	0	118/40	L. V. H.
J. A. D.	M	16	20	R.	+	+	+	108/48	N.
V. D. B.	F	12	27	R.	+	+	+	110/40	L. V. P.
J. A. F.	M	5	14	R.	+	0	0 - +	145/60	L. V. H.
R. L. J.	F	3	10	N.	+	0	+	112/50	C. H.
D. L. J.	F	3	15	R.	+	0	+	160/50	C. H.
P. K. C.	F	7	12	R.	+	0	+	100/70	L. V. H.

Key:
R.—Preoperative weight below the 16th percentile on the Iowa Weight Chart.
N.—Normal.
R. V. H.—Right ventricular hypertrophy.
L. V. H.—Left ventricular hypertrophy.
L. V. P.—Left ventricular preponderance.
C. H.—Combined hypertrophy.
E.—Enlarged.

(Fig. 5). The electrocardiograms reverted to normal or revealed less evidence of hypertrophy following operation. These changes occurred over varying time periods, generally requiring several months.

Cardiac catheterization and angiocardiography* were carried out in seven patients. In each instance the catheterization data were consistent with patent ductus arteriosus, and in five the ductus was entered. The diagnosis was confirmed by angiocardiography in three, and a retrograde aortogram was necessary for diagnosis in the ninth case. Three had associated mild pulmonary hypertension, three moderate, and one severe. There was some degree of reverse flow in two as evidenced by peripheral arterial oxygen saturations of 78 and 86 per cent. All were operated upon† successfully and are well or improving.

DISCUSSION

Uncomplicated patent ductus arteriosus usually is asymptomatic in infancy but, as illustrated by these patients, may be the cause of growth disturbances and/or cardiac failure. In general, the diagnosis before the development of the "typical" murmur is difficult and requires investigation by physiological methods. This difficulty is indicated by the clinical findings represented herein. The results of such physiological investigation were quite rewarding and the observation of ten such patients in four years indicates that symptomatic patent ductus arteriosus in infancy may be more common than heretofore appreciated. Surgical correction of this condition is at present the most satisfactory and least difficult procedure in the area of congenital heart disease in infancy.

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*Cardiac catheterization was performed by L. Leight, M.D., of the Department of Medicine, [illegible] by L. A. Davis, M.D., [illegible] Children's Hospital. [illegible] were described in a paper ("High Speed Biplane Selective Angiocardiography"), presented at the A. M. A. meeting June 4, 1957, New York City.

†Operations were performed by H. B. Lynn, M.D., Surgeon-in-Chief, Children's Hospital.

OF CLINICAL DATA

RADIOLOGICAL FINDINGS			PHYSIOLOGICAL STUDIES				
			CARDIAC CATHETERIZATION			CONTRAST	
CARDIAC SIZE	LEFT ATRIUM	PULMONARY VASCULARITY	CONCLUSION	P. A. P.	R. F.	SELECTIVE ANGIOCARDIOGRAPHY	RETROGRADE AORTOGRAPHY
E.	N.	I.					
E.	E.	I.	C.	49/32	+	N. D.	
E.	N.	I.					
E.	E.	I.	C.	41/19	0	N. D.	
N.	N.	N.-I.					
E.	E.	I.	C.	43/29	0	D.	
E.	E.	I.	C.	32/19	+	N. D.	
E.	E.	I.	C.	44/21	0	D.	
E.	E.	I.	C. (?)	87/50	0	N. D.	D.
E.	E.	I.	C.	61/48	0	D.	

I.—Increased.
C.—Confirmatory.
D.—Diagnostic.
P. A. P.—Pulmonary arterial pressure in mm. Hg.
R. F.—Evidence of reversal of flow through the ductus.
N. D.—Not diagnostic.

In those patients without a "typical" murmur, differential diagnosis in our experience was between an interventricular septal defect and patent ductus arteriosus. In retrospect, we have not been able to note any clinical findings that will aid in this differentiation. When confronted by this differential diagnosis in a symptomatic infant, physiological studies are justified, particularly in view of the recently reported[7] poor outlook of symptomatic infants with an uncorrected interventricular septal defect.

SUMMARY

1. Ten patients with symptomatic patent ductus arteriosus in infancy are reported and their clinical and laboratory findings summarized.

2. The importance of this congenital heart lesion is emphasized as a cause of growth retardation, pulmonary overcirculation, enlarged heart, and cardiac decompensation. In the majority, specific left atrial enlargement was also noted.

3. Cardiac catheterization, angiocardiography, and/or aortography is frequently necessary for the diagnosis of patent ductus arteriosus in patients prior to the development of a "typical" murmur.

4. Differential diagnosis in our experience rests between patent ductus arteriosus and interventricular septal defect.

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UNILATERAL RENAL VEIN THROMBOSIS IN AN INFANT WITH SEPSIS DUE TO SALMONELLA CHOLERAESUIS. NEPHRECTOMY WITH RECOVERY

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INTEREST in renal vein thrombosis has been renewed since 1942 when Campbell and Matthews[1] made the first preoperative diagnosis verified at operation. Several articles have since appeared dealing with the clinical and pathological aspects of this lesion, and there has been an increasing number of reports of patients successfully treated by surgery.[2]

Renal vein thrombosis in children is relatively common in the first months of life, especially in the newborn period, as a complication of diarrheal disease.[3] The process is either primary in the small radicles and extends secondarily into the main branches of the renal veins, or it occurs simultaneously in branches of small and large caliber.[4]

The main predisposing causes, in addition to ileocolitis associated with dehydration,[5] are sepsis, omphalitis, diphtheria, bronchopneumonia, skin infections, pharyngitis, and otitis. In these conditions the existence of vascular damage due to bacterial toxins is assumed.[6] Only in a few old reports[7] are bacteria reported as being cultured from the thrombosed veins.

The symptoms depend, to a certain degree, on the extent of the infarction and the survival time. In those cases diagnosed in life, the clinical picture is characterized by the sudden appearance in an infant with severe diarrhea and dehydration of a tender mass in either kidney region, by gross or microscopic hematuria, associated with albuminuria, pyuria, cylindruria, and sometimes oliguria or anuria, by azotemia, and, in some instances, shock. If the patient survives the initial period without surgery, the kidneys decrease in size and hematuria declines, although azotemia persists for some time.

The diagnosis is based on the previously mentioned data and is confirmed by intravenous pyelogram that shows exclusion of the diseased kidney. Retrograde urographic studies show incomplete or irregular filling of the renal pelvis on the affected side.

An early nephrectomy offers the greatest hope for recovery, due to the theoretical possibility of extension of the thrombus to the vena cava and opposite kidney.

The following case illustrates several of these points.

CASE REPORT

C. D. F., an 8-month-old male infant, was admitted to the Hospital Infantil de Mexico on Oct. 28, 1956, because of vomiting, diarrhea, and a fever of 3 days' duration. Previous history was noncontributory except for several mild bouts of diarrhea that improved spontaneously.

From the Hospital Infantil de México.

On October 25 the patient had passed 10 large watery stools, and in the next two days about 15 per day. High fever and occasional vomiting and coughing were present from the beginning, and he was restless and anorexic.

On admission the infant, weighing 6 kilograms, appeared acutely ill, and had a temperature of 38.7° C. He was semiconscious, dehydrated, with an acidotic type of respiration. The abdomen was soft and depressed, without masses on palpation. Deep tendon reflexes were hypoactive.

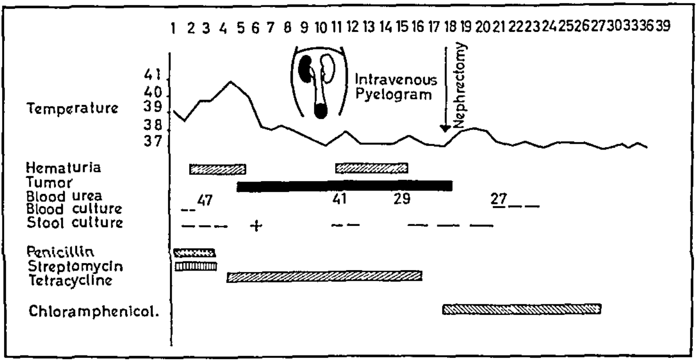

Fig 1.—Clinical course.

During the first week in the hospital (Fig. 1) the patient remained in a poor condition, with daily elevations of temperature to 39° or 40° C., pallor, dyspnea, dehydration, and restlessness. On October 29 gross hematuria was observed, continuing for 3 days. Blood pressure varied from 70/40 to 90/70. On November 1 a mass was palpated on the right flank; it was firm, smooth, measured about 8 by 4 cm., and was tender. In this period the number of stools were only 1 to 3 daily, most of them normal; there was no further vomiting.

Laboratory findings were as follows:

Hemogram on October 29 showed erythrocytes 3.64 million per cubic millimeter; hemoglobin 10 Gm.; leukocyte count 5,300 per cubic millimeter with a differential count of 76 per cent neutrophils, 22 per cent lymphocytes, and 2 per cent monocytes. Blood culture on October 29 was negative.

Urinalysis on October 31 showed albumin 2+, countless red blood cells and casts; on November 3, albumin 1±, no red blood cells or casts. Urine cultures on October 31 and November 3 were negative.

Blood chemistry on October 31 was: Blood urea, 47 mg. per 100 ml.; uric acid, 1.51 mg. per 100 ml., creatinine, 1.77 mg. per 100 ml.

Blood electrolytes on October 29 were: sodium, 151 mEq. per liter; potassium, 4 mEq. per liter; chlorides, 119 mEq. per liter; carbon dioxide content, 7.5 mEq. per liter; pH 7.08. On October 31 they were: sodium, 130 mEq. per liter; potassium, 3.25 mEq. per liter; chlorides, 107 mEq. per liter; carbon dioxide content, 22.5 mEq. per liter; pH, 7.44; calcium, 5 mEq. per liter.

Stool cultures on October 29, 30, 31, and November 7, 8, 12, 14, and 16 were negative. On November 2 *Salmonella choleraesuis* was cultured.

During the second week there was frank improvement. The temperature was never over 38° C., anorexia disappeared, hydration and consciousness became practically normal. The abdominal mass decreased in size. Urine was clear until November 7, when there was again hematuria, lasting this time for 4 days.

Urinalysis on November 7 showed albumin 1+, a few red and white blood cells, and casts.

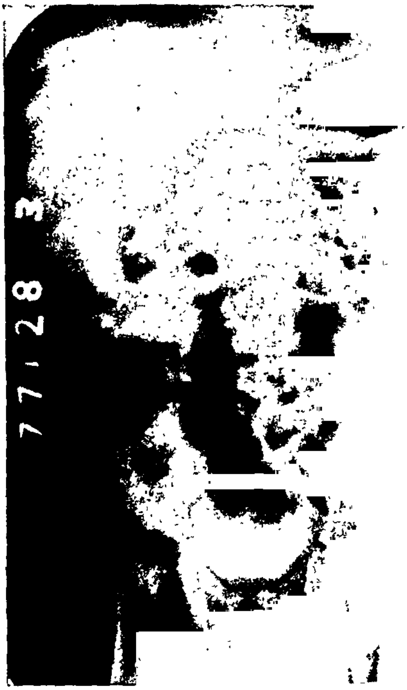

Fig. 2.

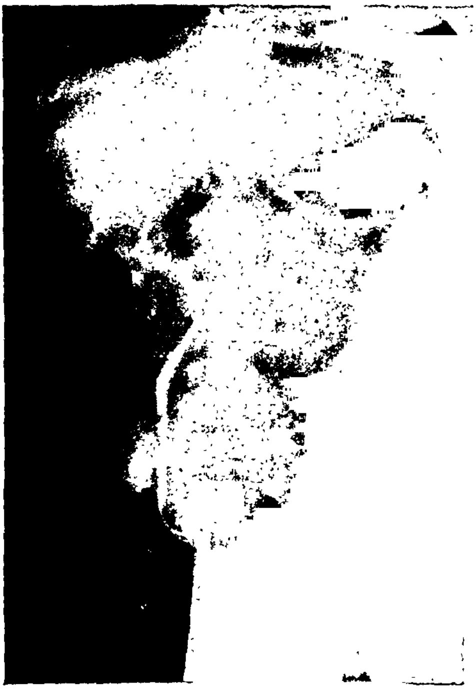

Fig. 3.

Fig. 2.—Intravenous pyelogram showing nonfunctioning right kidney with normal aspect of the left one.

Fig. 3.—Retrograde pyelogram showing displacement of the upper third of the right ureter and irregular filling of the renal pelvis.

Blood chemistry on November 6 was as follows: urea, 29.32 mg. per 100 ml.; uric acid, 1.16 mg. per 100 ml.; creatinine 0.92 mg. per 100 ml.

On November 7 an intravenous pyelogram revealed a nonfunctioning right kidney with normal left kidney (Fig. 2). On November 12 retrograde urographic studies showed the upper third of the ureter displaced by the enlarged kidney and faulty filling of the renal pelvis on the right (Fig. 3).

On November 12 surgical exploration was undertaken, with the diagnosis of right renal vein thrombosis. A right oblique renal incision was made. The kidney was enlarged, measuring 6 by 4 by 3.5 cm.; it was hemorrhagic and had small soft whitish-yellow nodules on its surface. Examination of the renal pedicle revealed that it was free of thrombus. The pedicle was dissected, doubly clamped and transected, and the kidney was removed. The pathological report described the size and outer aspect of the kidney. The capsule was 2 to 4 mm. thick and merged with the cortex. The kidney tissue was red and homogeneous. The renal pedicle was empty. Microscopic examination revealed necrosis of the renal tissue with only a few

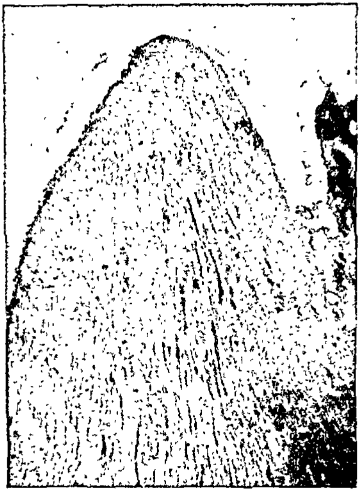

Fig. 4.—Photomicrograph showing total necrosis of the medullary portion of the kidney. (×21; reduced ⅙.)

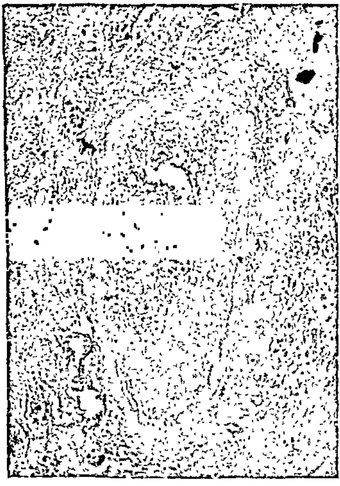

Fig. 5.

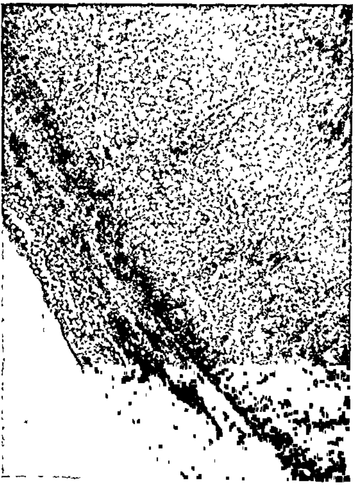

Fig. 6.

Fig. 5.—Photomicrograph of a thrombosed vein of the renal parenchyma. (×80; reduced ⅙.)

Fig. 6.—Photomicrograph demonstrating thickening of the capsule with lymphocytic infiltration. Notice a few tubules of normal aspect in the superficial portion of the cortex. (×80; reduced ⅙.)

tubules in the cortex (Fig. 4). In the medulla the veins were thrombosed (Figs. 5 and 6). Lymphocytic infiltration of the cortex and inflammatory infiltration with increased connective tissue in the perirenal tissue were noticed. Numerous colonies of *Sal. choleraesuis* were cultured on blood agar plates from a section of the kidney.

The postoperative course was uneventful. Urine and blood urea were normal; three blood cultures were negative.

The treatment during the first week consisted of intravenous electrolyte solutions (Darrow-glucose 5 per cent), blood and plasma. Intramuscular procaine penicillin was used during the first three days (October 28, 29, and 30) and after that intramuscular oxytetracyline (30 mg. per kilogram per day) for 5 days (October 31 to November 4) followed by tetracycline by mouth (50 mg. per kilogram per day) for 8 days more (November 5 to 12). Chloramphenicol was used immediately after surgery and maintained for 7 days (100 mg. per kilogram per day).

The child gained weight and was discharged cured on December 5.

COMMENTS

In the evaluation of the etiology it is important to take into consideration the action of the *S. choleraesuis* infection when added to the damaged kidney circulation affected by dehydration and shock, accompanying the severe enteritis. *Salmonella cholerasuis* is a well-known cause of sepsis and can produce acute pyelitis and pyelonephritis.[8] Nevertheless, so far as we have been able to determine, this is the first report in the literature where this organism was cultured from a thrombosed kidney. The fact that it was missed in the blood and urine cultures and that, of nine stool cultures only one was positive, emphasize the difficulties that similar cases may offer for the detection of the infectious agent. The advantages of direct culture from the kidney tissue for the discovery of infections have been observed by other workers.[9]

The sudden appearance of an abdominal mass with hematuria and azotemia in an infant with severe diarrhea forced us to consider the possibility of renal thrombosis. This was made evident by the x-ray studies. Improvement was remarkable. In a few days, despite the complete destruction of the right kidney and the existence of a salmonella infection within it, there was no fever, the kidney became progressively smaller, hematuria disappeared, and blood urea tended to become normal. Probably, some unilateral cases where hematuria and kidney enlargement are of a lesser degree might pass unnoticed during the acute stage, with the possibility of hypertension being caused in later life.

To avoid the extension of the thrombus to the vena cava and to the other renal vein, an immediate operation has been advised. However, consideration should be given to improvement of the condition of infection, shock, dehydration, and acidosis, especially because the mechanism of production does not depend as much on the presence of a previous thrombus as on the existence of a mechanism that favors its development.

SUMMARY

Unilateral renal vein thrombosis following a severe *Salmonella choleraesuis* enteritis is reported in an 8-month-old infant. Clinical and radiological data brought about the recognition of this disease. The diagnosis was confirmed at operation. *S. choleraesuis*

was cultured from the kidney. The patient recovered after nephrectomy.

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GIANT HEMANGIOENDOTHELIOMA WITH ASSOCIATED THROMBOCYTOPENIA

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FOURTEEN cases of thrombocytopenia with large hemangiomas have been reported since the original description by Kasabach and Merritt in 1940.[1-10] Of these 14 patients, two died as a result of the disease, one from hemorrhage into the thoracic cavity[3] and the other from asphyxia secondary to hemorrhage into a hemagioma of the neck.[7] A third child died from an overwhelming infection[8] several months after splenectomy. The remaining 11 had regression of the tumor, either spontaneously or following radiation, accompanied by return to normal of the platelet counts and subsidence of the hemorrhagic manifestations.

The characteristics common to all these cases were (1) a large vascular tumor involving a fairly large area, such as a shoulder, an arm, a leg, the abdomen, the thorax, the head, or the neck, (2) thrombocytopenia, (3) clinical evidence of hemorrhage into the tumor with ecchymoses and petechia elsewhere, and (4) anemia, secondary to hemorrhage into the tissues.

Thirteen of the 14 patients had had the full syndrome before the age of 1 year. Most of the 13 were hospitalized for therapy before the age of 3 months.

Our case is presented to demonstrate a successful program of therapy combining radiation, Meticorten (prednisone), and whole-blood transfusions.

CASE HISTORY

This 1-year-old white girl was admitted to a United States Army Hospital at Camp Zama, Japan, on July 25, 1956, with a large ecchymotic area on her right breast and anterior chest wall which had been noted three days before admission. Chest x-ray at this time revealed the right hemidiaphragm to be markedly elevated, and a band of increased density extended along the lateral chest wall which appeared to represent pleural fluid. Coarse trabeculations of the right upper ribs with decalcification and periosteal reactions were noted, suggesting either inflammatory or neoplastic changes. Long bone studies of the upper and lower extremities were normal. Bleeding time was 1 minute 45 seconds; coagulation time was 4 minutes 30 seconds. Rumpel-Leede tests were negative. Platelet count was 164,000 on one occasion. Bone marrow study on July 31 was normal. Thoracentesis was performed during this admission and grossly bloody fluid was obtained. On August 21 the child was transferred to Tokyo Army Hospital for thoracic surgery consultation to determine the type of neoplasm on the right side of her chest. On August 27 a biopsy of both soft tissue and rib was performed. From the biopsy material a diagnosis of hemangioma of the capillary type, "hemangioendothelioma," was made. The child was transferred to Walter Reed Army Hospital for further treatment. During her trip by air evacuation to this hospital there was a noticeable increase in the size of the right side of her chest wall accompanied by further ecchymoses, mild respiratory distress, and anorexia.

From the Pediatrics Section, Walter Reed Army Hospital, WRAMC.

Family History.—The father and mother, aged 25 and 26, respectively, are alive and well. The child was the product of a normal pregnancy and delivery. Family history was negative for disease tendencies except for diabetes in a maternal grandmother.

Past history was not remarkable for any illnesses other than an occasional upper respiratory infection.

Physical examination on September 19 revealed a well-developed, well-nourished child in moderate respiratory distress. Her weight was 25 pounds. There was a diffuse swelling covered with ecchymoses over the right anterior chest wall. The swelling was soft and nontender. No bruits could be heard or thrills felt in the mass. There were strong breath sounds in the left lung field and no râles could be detected. Voice and tactile fremitus were normal on the left. Over the right lung field the breath sounds were decreased and percussion note was dull. Vocal fremitus was increased on the right. Blood pressure in the right arm was 88/54. Point of maximum impulse was in the sixth intercostal space between the midclavicular line and the anterior axillary line. Trachea appeared deviated to the left. Pulse rate was 90 per minute and regular. A_2 and P_2 were equal. Liver was palpable 2.5 cm. below the right costal margin. The spleen could not be palpated. Extremities showed no deformities. Genitalia and rectum were normal. Neuromuscular examination was within normal limits.

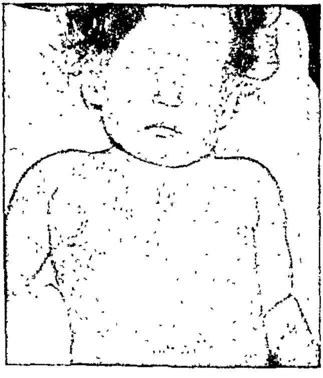

Fig. 1.—Photograph of patient made on admission to Walter Reed Army Hospital, showing ecchymoses and area of involvement of the hemangioendothelioma.

Laboratory Data.—On admission the white blood cell count was 15,000 with 56 neutrophils, 42 lymphocytes, and 2 monocytes. Hemoglobin was 9 Gm.; hematocrit was 26 per cent. Urinalysis was negative. Chest x-ray showed that the entire right pleural space was obscured and clouded, and no area of the lung could be demonstrated. The heart shadow appeared to be slightly displaced to the left side. In the lateral views the architecture of the lung fields anteriorly was obscured by what appeared to be a large tumor mass. However, the posterior costophrenic sulcus was clear. The interpretation was that a significant amount of pleural fluid was present in the right side of the chest, but that the main opacification was probably secondary to a tumor mass. It was also noted on the x-rays that the first six ribs on the right side appeared to be involved by a diffuse bone destructive process.

Hospital Course.—It was felt on admission that the child was critically ill and the prognosis for life was poor. The general appearance was that of a malignant process, even though the biopsy diagnosis had been hemangioendothelioma. A bone marrow examination was done to see if diffuse process could be demonstrated. Following the bone marrow aspiration on September 21, the child continued to bleed from the aspiration site for about eight hours. Platelet count was performed and revealed a count of 8,000 platelets per cubic millimeter. This platelet count and all subsequent counts were performed by the direct phase microscopy method. Smears from the tibial marrow aspirate were quite cellular. There were many small mature lymphocytes throughout the marrow

(41 per cent). Granulocytes were frequently seen and showed normal maturation with a borderline increase in the eosinophils. The total number of erythroid cells was reduced. Maturation, however, was normal with good hemoglobinization. The total number of megakaryocytes was increased and many of the megakaryocytes had granular cytoplasm and lobulated nuclei. A few had some platelets near the borders. Some of the megakaryocytes did not have granules in the cytoplasm and/or had evacuated cytoplasm. The number of agranular megakaryocytes, however, was small. The marrow was not specific for any disease, but it was compatible with thrombocytopenia secondary to rapid removal of platelets from the peripheral blood. On September 22 the child was given 10 mg. of Meticorten in divided doses. Twenty-four hours later the platelet count was 42,000. The child was seen by the Tumor Board and they unanimously recommended that she be treated with irradiation. On September 23 irradiation was started with 100 roentgens. During the next 31 days the child was to receive a total dosage of 2,000 roentgens tumor dose through 10 by 15 cm. anterior right hemithorax port and 10 by 10 cm. posterior right hemithorax port. Six days after initiation of therapy the platelet count was 610,000. Because we did not know whether or not Meticorten had any effect on the platelet levels, we discontinued the Meticorten therapy and continued to give radiation. The child's condition improved. She was breathing without distress and the ecchymotic areas were disappearing. The chest x-rays, however, continued to be formidable and showed the tumor mass involving the chest wall and ribs on the right side with evidence of rather massive pleural effusion on the right. The case was discussed with thoracic surgeons who felt that no vigorous attempt should be made to perform a thoracentesis. The patient had improved so much clinically that it was decided to allow her to return home with her parents and to have radiation as needed on an outpatient basis to complete the course of 2,000 roentgens. The parents were instructed that the child was to return immediately if there was any increase in respiratory distress or any further evidence of bleeding.

Five days after discharge, this 15-month-old child was readmitted to Walter Reed Army Hospital because of the sudden development of shortness of breath beginning early on the morning of admission. Coughing was also noted which was more severe than usual. There was no hemoptysis. At the same time the parents noted that the right anterior chest wall appeared to be more prominent and swollen. The admission platelet count was 18,500. Hemoglobin was 14.1 Gm. with a hematocrit of 48. Because of the immediate deterioration since steroid therapy, it was felt that Meticorten was needed and that radiation therapy alone was not enough to control the thrombocytopenia in this patient. Accordingly, she was started on a 15 mg. divided dose of Meticorten daily, decreasing gradually to a maintenance dose of 7.5 mg. daily. Over the next week after admission the child had evidence of a superimposed respiratory infection in addition to her underlying disease. She responded slowly but steadily to antibiotics after treatment with oxygen and moist air. Increase in her platelet counts, however, was gradual. The second platelet count on the day of admission showed a further drop to 7,500 platelets. By October 15, on the sixth day after her second admission, the platelet count increased to 42,000. On October 16, the platelet count was 130,500. At this point radiation therapy was reinstituted. During the second hospitalization she received transfusions of whole fresh blood from a silicone-treated plastic bag. By October 20, the child's condition had improved clinically and she was more alert and active. There was a noticeable decrease in the size of the mass in the right side of the chest and approximately 75 per cent regression of the tumor of the soft tissues by x-ray. The child was discharged from the hospital on October 25, 36 days after her initial admission. She was seen frequently as an outpatient and platelet counts were obtained at weekly intervals for two months. Meticorten was continued in gradually decreasing dosages for 2½ months following discharge. Since complete withdrawal of Meticorten on Feb. 10, 1957, the child has shown no recurrence of the tumor and has had normal platelet counts.

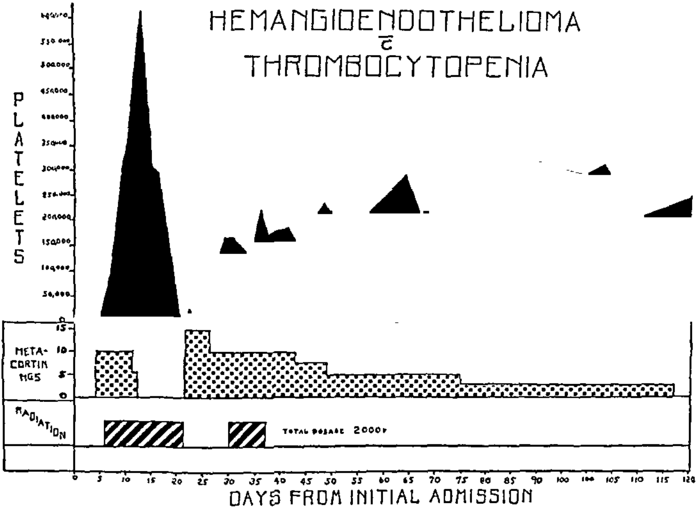

Fig. 2.—This chart illustrates the relation of the prednisone and radiation therapy to the platelet counts in this patient. Note rise in platelet counts with prednisone therapy prior to both courses of radiation therapy.

COMMENT

Fourteen cases of large hemangiomata with associated thrombocytopenia have appeared in the world medical literature since 1940.[1-10] Management of these patients had included radiation therapy, splenectomy, blood transfusions, and in one case, steroid therapy. Splenectomy was thought to be of real value in one of the five patients in which it was performed.[9] In this patient, however, the platelet response did not appear until one week after splenectomy. In addition, the child had had radiation to the tumor shortly before the surgery, and the hemangioma was secondarily infected. The one patient treated with a steroid (cortisone) received small doses of 25 mg. daily for a three-day period.[9] No effect on the platelet count was noted.

In spite of a well-established clinical association between these two disorders, the exact relationship between the thrombocytopenia and the hemangioma remains obscure. Good[8] suggests that sequestration, utilization, and destruction of platelets occurs within the hemangioma teleologically in the host's attempt to destroy the tumor. Platelet thrombi form within the capillaries of the hemangioma, thus producing vascular occlusion. His concept is that the tumor acts to filter the platelets, thus removing them from the blood stream. The marrow responds by hyperplasia, but in a small child with a large tumor, the hemopoietic system is unable to meet the demands of both the tumor and the peripheral blood for platelets.

In support of this concept, in our patient and in the other reported cases, the regression of the hemangiomas seemed directly related to the return of the platelet counts to normal. We also noted a rise in platelet counts with Meticorten therapy which was independent of radiation treatment (Fig. 2). This may represent an inhibiting effect of Meticorten within the hemangioma, preventing the sequestration of platelets and the formation of platelet thrombi. This is the first reported case in which this effect has been noted.

This process of endothelial hyperplasia, the formation of platelet thrombi with resultant vascular occlusion, and the regression of the tumor may be the "normal" way for the destruction of hemangiomas. We have all seen the spontaneous regression of small untreated hemangiomas of the skin. Perhaps this disorder is much more common than is realized, for thrombocytopenia can exist without bleeding tendencies. Unless these two phenomena are associated, the possibility of thrombocytopenia might not be considered when a large hemangioma regresses without complications.

SUMMARY

The fifteenth case of giant hemangioma with associated thrombocytopenic purpura is presented. This patient was successfully treated with radiation, prednisone, and whole blood transfusions. Although the ultimate cure of this disorder resulted from the destruction of the tumor by radiation, the effect of the use of prednisone on this patient was lifesaving in preventing the destruction of platelets during the interim between radiation and the effects of radiation on the hemangioendothelioma. This is the first reported case in which this effect of prednisone has been noted with this syndrome.

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Clinical Pathological Conference

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SIDNEY FARBER, EDITOR
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THIS 9½-year-old boy, who had always been considered to be in excellent health, during a routine school physical examination was found to have hypertension, with a blood pressure differential between the arms and legs, and a heart murmur.

After a visit to the Cardiology Clinic, he was admitted to the Surgical Service. Here his initial physical examination showed him to be a well-developed and apparently healthy boy in the tenth and twenty-fifth percentile for height and weight. His temperature, pulse, and respirations were normal. The blood pressure was recorded as 140 mm. Hg systolic and 94 diastolic, in the arms; that in the legs was unobtainable. No femoral pulse was elicited. No cyanosis, clubbing, edema, or chest deformity was seen. The heart was slightly enlarged, had a normal rhythm, and the aortic and pulmonic second sounds were equal. A grade IV systolic plateau murmur was heard over the entire precordium, with a maximal intensity in the second intercostal space at the right sternal border. There were no abnormal findings in the abdomen.

The laboratory examinations on admission showed normal urine, a hemoglobin of 13.5 gm. per cent, and a leukocyte count of 8.1 thousand per cubic millimeter. The serum nonprotein nitrogen was 35 mg. per cent. The roentgenographic examination of the chest revealed the heart to be slightly enlarged, with a rounded apex and an indentation of the esophagus by the aortic arch on barium swallow. The electrocardiogram demonstrated a sinus arrhythmia, and a left axis deviation. The latter was interpreted as evidence of left ventricular hypertrophy, abnormal for the age.

On the third hospital day, a coarctation with a 2 mm. lumen in the narrowest segment was removed uneventfully. At operation no thrill could be palpated over the heart, though the left ventricle was enlarged. A measured blood loss of 500 c.c. was replaced.

The postoperative course was complicated by apprehension, urticaria, convulsions, hypertension, and electrolyte imbalance. The blood pressure 24 hours after operation was 128 mm. Hg systolic and 100 diastolic in the arms, and 150 mm. Hg systolic and 114 diastolic in the legs. Four days after the operation the patient was ambulatory. After ten days the pressure rose to 170 mm. Hg systolic and 140 diastolic, and 190 mm. Hg systolic and 134 diastolic, respectively. The femoral pulses remained full and bounding.

Because of the development of urticaria, penicillin was discontinued and tetracycline substituted; the urticaria disappeared six hours after the administration of triphenamine hydrochloride. Vomiting, 2 to 3 times daily, persisted despite medication.

The evening before his expected discharge on the tenth hospital day, he developed a right-sided grand mal seizure which lasted eight minutes but was controlled after intravenous sodium Amytal. A transient residual paralysis cleared the following morning. Skull films and lumbar puncture at this time were normal. The electroencephalogram showed a slowed and disorganized pattern with left-sided predominance.

He was placed on Dilantin and phenobarbital and discharged home on the sixteenth hospital day, asymptomatic and afebrile.

On the nineteenth postoperative day he was readmitted with a history of anorexia for two days, nausea and listlessness progressing to disorientation and delirium. A generalized convulsion occurred immediately before admission; a second convulsion on admission was stopped with intravenous Amytal. Neurological examination was again noncontributory for localizing signs. Over the next forty-eight hours he passed several foul-smelling, grossly bloody stools, which then cleared; during this period he had mild generalized abdominal tenderness but no spasm.

The laboratory examinations now showed many erythrocytes in the urine. The peripheral leukocytes numbered 87.0 thousand per cubic millimeter, with 96 per cent polymorphonuclear leukocytes on differential smear. The blood chemistry values were as follows: nonprotein nitrogen 50 and fasting blood sugar 235 mg. per cent; pH 7.35; carbon dioxide content 3.5 sodium 127, potassium 5.1, and chlorides 57 mEq. per liter; 17-hydroxycorticoids 43 μg per cent (normal below 25 μg per cent).

Vigorous but unsuccessful attempts were made to correct the electrolyte deficiency with as much as 2,500 ml. of saline and 60 mEq. of potassium chloride being given daily. After twelve days of vigorous therapy to a seemingly moribund patient, the blood chemistry values were: nonprotein nitrogen 44 mg. per ment, pH 7.32, carbon dioxide content 35.3, sodium 117, potassium 4.8, and chloride 72.5 mEq. per liter. The leukocyte count remained between 30 and 80 thousand. An example of several quantitative twenty-four hour urine collections showed sodium 79, chloride 87, and potassium 44 mEq. Antibiotics and anticonvulsants, electrolyte and blood transfusions were given.

Abdominal tenderness gradually increased in severity and thirty-one days after the original operation, an abdominal operation was performed. The subsequent improvement was slow but gradual and he was discharged home, one month after the second operation.

DISCUSSION

DR. CHILTON CRANE.*—First, we note that two maternal uncles had epilepsy. I think that we have to bear this in mind in view of later events, and that we have to say that this boy probably had some sort of predisposition or lowered threshold which caused him to have episodes of convulsions on relatively minor stimuli which would not occur in an otherwise normal individual. There was a grade IV systolic stenotic murmur which was heard over the entire precordium with maximum intensity at the second intercostal space at the right sternal border. This would certainly put this murmur, from the point of view of location, at the aortic valve. It is hard to believe that he had a very high degree of aortic stenosis in view of the hypertensive pressures which he later developed.

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The serum nonprotein nitrogen is 35 mg. per cent which appears to be a little on the high side. If it is truly elevated, we can assume right away that he has an underlying serious renal disease. If there is any elevation in the steady state of the nonprotein or urea nitrogen, we can assume that 75 per cent or more of the nephrons have already been injured.

A typical coarctation of the aorta was encountered, with a 2 mm. opening through the narrowed segment. A "typical coarctation," I am certain, is one which is distal to the left subclavian vessel, as are 97 per cent. We must assume that this 2 mm. opening through the coarctation is rather larger than many. Claggett[1] who examined, with Edwards, 124 specimens removed at operation, found that most of the openings were smaller than 2 mm. in diameter. The only conceivable importance of this is in relation to the question of interference with renal flow, which might have occurred during the brief period of clamping of the aorta. This question of adequate renal blood flow very rarely becomes a problem in coarctation cases because renal hypoxia, related to obstruction of vessels during operation for this particular lesion, is probably nonexistent, simply because of the tremendous collateral blood flow.

There was a measured blood loss of 500 c.c. which was replaced during the operation. I think that we can assume from this statement that there was no cause for hypotension during operation and that oliguria was not a feature of the postoperative course. I am trying hard to find some cause for this individual having developed a renal lesion *which I feel quite certain he* did have. I do not think that we have any evidence that the surgery *per se* induced changes in renal blood flow or effective blood pressure which, in turn, caused the possible later renal difficulty.

Very interestingly, we note that the initial postoperative blood pressures *in the arms were, as expected, 128/100* —still somewhat elevated—but instead of going down further to normal over the next few days and weeks, they gradually rose after ten days to 170 systolic and 140 diastolic and, very important, the lower-extremity blood pressures also rose to 190 systolic and 134 diastolic after ten days. The femoral pulses remained full and bounding subsequent to this operation, which tells us, of course, that the aortic repair was a completely adequate one, that he had an excellent lumen through the aorta, and that the subsequent elevation of blood pressure was unrelated to any block in the major arterial pathway. This suggests that the hypertension had a renal origin, or that there was a remote possibility of a pheochromocytoma. One might speculate that if a pheochromocytoma were present with a coarctation and an enhanced flow was produced after repair, this might induce increased activity on the part of the tumor. Pheochromocytomas are apparently extremely sensitive to changes in both blood pressure and flow, so one might have a considerable functional response with a resulting great elevation of blood pressure. I cannot take this seriously, however, because this should have occurred immediately postoperatively with a labile type of hypertension. This rise occurred gradually, steadily, and slowly over the course of ten days.

Vomiting persisted two or three times daily for ten days, in spite of Thorazine and antacid therapy. If this individual really continued to vomit fairly large volumes of gastric contents over ten days, it would be important in his subsequent electrolyte status, after his second admission—but I cannot believe that the vomiting was significant in amount or he would not have been in sufficiently good condition to go home on the tenth postoperative day.

The evening before his discharge he developed a right-sided grand mal seizure, lasting eight minutes. Now this seems important, yet the transient residual right semiparesis had cleared by the following day. This seems to tell us that this was not a pure epileptiform episode, but that actual brain damage was responsible for this neurological defect. I think it must be put into the category of thrombosis or hemorrhage into the brain substance.

After his re-entry, he developed bloody diarrhea, but we are not told how long this diarrhea persisted. This might be important in regard to both his later electrolyte pattern and his intra-abdominal problem.

The hydroxycorticoids were 43.7 μg per cent and we are told that the normal level is under 25. This tells us that the adrenal cortex is operating normally, and that the cause of the salt-losing renal lesion is not adrenal failure. It suggests that the anterior pituitary is functioning and that he is pouring out corticoids at a high level. Vigorous attempts were made to correct the electrolyte deficit, but were unsuccessful. After twelve days of such vigorous therapy to a seemingly moribund patient, the nonprotein nitrogen was 44 mg. per cent. This means, I should think, that he was putting out good urine volume right along because he successfully cleared his nonprotein nitrogen. It would be helpful to know the urine sodium levels in collections made when no intravenous saline was being administered. If, for example, urine sodium levels were high when he was not receiving any intravenous sodium, we could surmise that sodium was readily passing through the kidney and that there must be a tubular lesion of some significance since he was unable to conserve sodium. If the kidneys were normal, one would assume that the sodium excreted would amount to only 1 or 2 mEq. per twenty-four hours. As we mentioned, the adrenal cortex was normal, so that apparently does not enter here. If anything, the adrenal should conserve sodium. So, we conclude, I think, fitting in the red cells in the urine, the rising nonprotein nitrogen, and so on, that he had a significant and quite severe renal lesion with a salt-losing ingredient mixed into it. With these low levels of sodium and chloride, we think of water retention, particularly in individuals with a renal lesion. We do not know whether he was losing weight as he should have been, day after day, and what his intake and output were, but he was certainly having good urinary output, and I doubt if water-loading was present. I doubt that he became edematous or that he was gaining weight. He had all the background of stress and sepsis for a sodium-potassium shift with sodium going into the cells and the postassium coming out. When the infection was cared for, he presumably improved in this regard.

The white count remained between 30,000 and 80,000. This alone makes one think of three situations: (1) very diffuse sepsis; (2) a very large area of necrosis, as though a long segment of intestine were slowly becoming nonviable with much tissue death; (3) perhaps a leukemoid type of reaction or an unusual response which is seen in miliary tuberculosis, typhoid fever, and other infections.

Abdominal tenderness gradually became a more prominent feature of the illness, and on the twelfth hospital day (thirty-one days after the original surgery) an operation was performed. This abdominal tenderness is most important because here, in the march of events in this patient, the evidence finally indicates that he has a serious intra-abdominal trouble which is promoting the electrolyte imbalance and is making him profoundly ill. Treatment for this may save the patient. From the record it appears that the abdomen became more and more tender, until it became obvious that there was diffuse intraperitoneal irritation and, almost certainly, intraperitoneal sepsis.

May we now see the x-rays, particularly those of the chest and the abdomen, if any were made prior to this operation.

Dr. E. B. D. Neuhauser.—In the film of the chest made before operation, at the time of the diagnosis of coarctation, he had a considerably enlarged heart with left ventricular enlargement and hypertrophy. There was no rib notching. This shows very beautifully again with barium swallow and there was, in the oblique projection, indentation of the esophagus produced by the aortic arch shown beautifully by a barium swallow. There was much post-stenotic dilatation of the aorta. In the postoperative film the heart appeared very much smaller, which probably represents a change in blood volume rather than in cardiac mass. The first film of the abdomen was made when there was great abdominal distention. The stomach was dilated and nearly all of the distended loops were in the small bowel, but there was some gas in the colon. The bowel loops appeared to be slightly separated, and we interpreted that to be caused by either a small amount of free fluid within the peritoneal cavity, or actual edema of the adjacent bowel walls, producing a thicker shadow than one would normally get.

Dr. Crane.—You would conclude, Dr. Neuhauser, with what you see there, that this is diffuse—that there is no obstructive point?

Dr. Neuhauser.—We could not define a single obstructive point and we thought that this was a diffuse lesion. The upright film showed perhaps more strikingly the disturbance of the motor function, with dilated loops related to fluid levels.

Dr. Crane.—It seems to me that what we have to try to explain in this extraordinary sequence of events is three lesions on the basis of a single set of circumstances: a cerebral lesion—either a hemorrhage or an abscess; a renal lesion—either pyelonephritis or acute glomerulonephritis; and a lesion of the gastrointestinal tract, which developed to the point of multiple dilated loops with fluid, accompanied by diffuse abdominal tenderness, resulting in generalized peritonitis secondary to the lesion of the intestine.

In trying to coordinate the factors in this case I could not help wondering whether subacute bacterial endocarditis could enter into this on the basis of the aortic murmur, and the fact that some people with coarctations do have other anomalies of the great vessels of the heart, and that such lesions are so often unsuspected. Could he thus have had emboli to the brain, the kidney, and the intestine? A loop, or several loops, of small bowel may have been barely viable over a period of days, but I have just not heard of this taking place in subacute bacterial endocarditis. I think the remarkable shrinkage of the heart suggests that the cardiac findings were almost solely related to the coarctation and that probably no significant valvular aortic lesion was present.

Could all of this be explained on the basis of acute renal failure? Underlying renal disease in the form of a chronic yet compensated glomerular nephritis might be made worse by the stress of surgery, and the clamping of the aorta, which normally would have no effect at all, might, with such a series of events, produce renal failure, so that the patient developed hypertension and then subsequently developed uremic ulceration of the bowel. Uremic ulcerations of the intestine do not usually occur with a nonprotein nitrogen level of 55 mg. per cent. They are usually terminal, and I am not familiar with perforations of uremic intestinal ulcer. We have no evidence with which to localize the bleeding, but since the blood he passed was not fresh, we can assume it was not from the colon. I do not believe that such a formulation explains the intra-abdominal problem, but it may have contributed to the cerebral symptoms as a hypertensive encephalopathy associated with convulsions.

Could all this represent a staphylococcal enteritis with perforation and septicemia? The frequency of bowel movement cased off very quickly and sepsis appears more important. We have no knowledge of positive cultures for staphylococci in the blood or feces. Staphylococcal enteritis would not cause hypertension.

I considered acute polyarteritis, with involvement of brain, kidney, and intestine, but I discarded that as unlikely.

My final diagnoses are: (1) hypertensive encephalopathy, on a background of epilepsy, with a question of staphylococcal abscess in the left hemisphere; (2) acute pyelonephritis superimposed on an old glomerulonephritis with renal failure; (3) a perforation of the gastrointestinal tract—either a perforated duodenal ulcer coming on in the wake of the high corticoid levels, or an acute perforation of the right colon on the basis of an acute ulcerative colitis. I believe, in any event, that the operation consisted of drainage of a generalized peritonitis and of dealing with a perforation in the gastrointestinal tract. This would involve a simple closure of the duodenum and, in relation to a perforation of the colon, probably an ileostomy.

DR. JOHN F. CRIGLER.—The more I look over the protocol and see the disconnected information given to Dr. Crane, the more I sympathize with him.

One of the reasons that I was called to see this patient was to determine whether he was to be given cortisone, and that was the reason why the corticoid level was determined. He apparently was very ill but he was not hypocorticoid. As far as the electrolyte disturbance was concerned, I was quite certain that it was not due to adrenal insufficiency, even before the corticoid levels were drawn. It seems that it was due to his intestinal difficulty. He was treated intensively with much salt, water, and cortisone. Urine specimens were obtained at random to determine the amount of salt excreted. I did not think that he had evidence of renal damage prior to his operation, or during his postoperative complications here, but I think that is because I did not consider a nonprotein nitrogen of 35 as abnormal.

My general impression of the patient's illness was that he had a diffuse embolic, septic process, associated with the postoperative course of the repair of a coarctation. He did have signs of intracranial, intestinal, and renal difficulty. The surgery performed was, I think, wisely done, although I did not go into the possible pathology at the time. I cannot disagree with Dr. Crane's analysis of the case.

DR. ROBERT E. GROSS.—We of the Surgical Service came to the same conclusions as Dr. Crane and Dr. Crigler—that this whole process might best be explained on the basis of sepsis. Endocarditis, with infection beginning at the suture line, was one of the important considerations, but we were never able to prove this, though multiple attempts to do so were made.

At the second operation there were multiple areas throughout the small intestine which appeared to be gangrenous. Some of these appeared about to perforate. One segment of bowel, about 15 inches in length, was exteriorized because we realized that this part of the intestine was the worst at the time, but there were dozens of other similar areas scattered throughout the intestine which might also perforate. His Mikulicz ileostomy was subsequently closed and he was discharged from the hospital. We feel that he will have no more trouble with the intestine.

There is still some vascular disorder present because this boy still has hypertension. He has no block in the aorta because the blood pressure in the legs is recorded as higher than in the arms, yet this individual's response is altered, either because of a diffuse arteriolar spasm, arteriolitis, or arteritis, which is still maintaining the blood pressure above normal. Whether this is going to subside in time, we do not know. We have seen a half dozen patients who, following operation for coarctation, did not get relief of their hypertension for a period of many months. We do not understand what happened in these patients.

DR. CRAIG.—Did those patients have a fall in blood pressure? This patient's pressure fell after operation, and then went back up again.

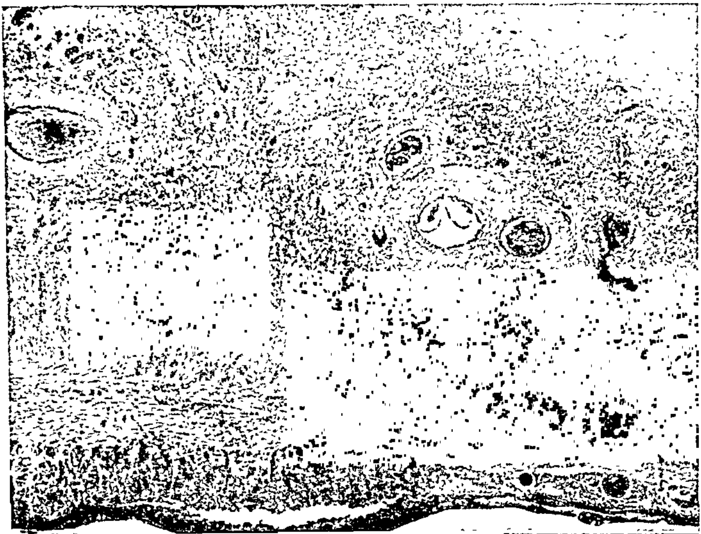
Dr. Gross.—It fell some, initially, but it certainly did not come down to the level we would like to have seen.

Dr. Craig.—The bowel wall was indeed, as Dr. Gross stated, gangrenous in appearance, partially filled with fluid, with many areas of gross mucosal ulcerations. The essential lesion was one involving medium- and small-size arterial vessels. They were involved in an acute arteritis with fibrin deposits in the intima, fibrinoid necrosis of the media, and periarterial inflammation. Organization of the central fibrin masses then led to occlusion of the vessels, with resulting infarctive necrosis of the surrounding tissue, especially the mucosa (Figs. 1 and 2). The lesion appeared to be limited to arteries and did not affect veins, so is not to be regarded as a diffuse vasculitis. No emboli were identified, the earliest lesion always being related to the intima. This type of change was present throughout all the sections of the removed portion of intestine.

There have been five or six recorded cases with similar histories and findings.[2-5] Such a patient, with hypertension associated with a coarctation of the aorta, has an excision, which is followed by an asymptomatic interval of a week or two, and then a return of the hypertension, but now of the lower body as well as the upper, and the development of abdominal pain, distention, and intestinal obstruction. Finally, gangrene of the bowel may occur, involving perhaps only a 10 to 12 cm. segment, or in severe cases, the entire small intestine. In one autopsied case in a 26-year-old man, the changes seen in the arterial vessels of the intestine of this case, were present in all the small arteries below the point of the coarctation, in the mammary, intercostal, hepatic, and renal arteries, with numerous associated infarcts.[2] One boy developed an aneurysm in the splenic artery; this ruptured, causing his death by intraperitoneal hemorrhage.[3] In none of the described cases were arterial lesions present above the level of the coarctation. In some of the described cases there was, fortunately, a limited area of involvement of the intestine. In them, prompt recognition and excision of the segment were lifesaving. Most of the surviving patients have not had a persistence of the hypertension, as this boy apparently has, though it has taken several months for the blood pressure to return to normal.

The etiology of this lesion, I think, is one for great debate and the fundamental problem is whether hypertension itself will give rise to periarteritis. This is distinct from the small arteriolar necrosis that one encounters in essential hypertension. Dr. Pearl Zeek,[6] who has worked in this field for a long period of time, in a review in the *New England Journal of Medicine* in April, 1953, came to the conclusion that there is quite definite evidence that in certain situations hypertension alone will give rise to the classical picture that we see histologically in periarteritis nodosa. One very striking experiment is the simple isolation of a segment of an artery, the injection in that portion of a fluid under greatly increased pressure, the releasing of this pressure, and the sacrificing of this animal a few days later. In such isolated segments of artery, there is a striking histologic picture of periarteritis nodosa without involvement of other vessels, an indication that the etiological agent is not

Fig. 1.



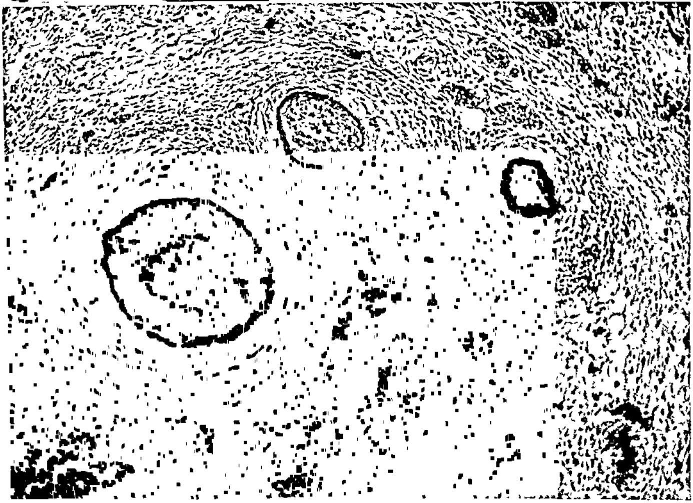


Fig. 2.

Fig. 1.—Photomicrograph, intestine. The lamina propia is necrotic; arteritis and obliterative thrombosis are present in the submucosal vessels; there is hemorrhage in the serosa. (Toluidine blue eosin. ×35.)

Fig. 2.—Photomicrograph, intestine. Periarteritis, fibrinoid necrosis, fibrin deposition, and organizing obliterative endarteritis are present in the submucosal arterioles. (Toluidine blue eosin. ×140.)

always a circulating toxin produced by partial occlusion of the renal arteries, by placement of cellophane about the kidney, or by induction of hypersensitivity.

It appears that the lesion in these patients is somehow related to the sudden change in blood pressure in the areas below the coarctation, after its excision. It is interesting to note that one of the children (a 4-year-old boy who survived) also had the low serum electrolyte pattern that was described during this patient's course. The renal lesions described at autopsy in such cases require much study for correct interpretation of their clinical pathologic correlations.

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Medical Progress

REFLECTIONS ON INFANTILE GASTROENTERITIS AND ITS TREATMENT

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". . . my bowels are troubled, my liver is poured upon the earth. . . ."
Lam. 2:11.

ABOUT 2,500 years ago, a physician from Babylo-Assyria pronounced some weighty opinions on diarrhea: "If a man has a pain in his stomach and cannot retain food, which comes back through the mouth, and his bowels are loose, and he vomits . . . and diarrhoea has set in. . ." then, states he, therapy was to be dispensed in the form of a medication and incantation in order to dispel the demon responsible for the disease. A representative sample of such therapy is: "slaughter a kurku bird, take its blood, fat, and the skin of its crop, burn it in the fire, mix cedar with the blood, and pronounce three times the incantation known as 'evil finger of man.' "[1]

Among the ancients, the concept of animism pervaded all thought. It was believed that anything which moved, anything that possessed power, must be alive. The rustle of trees, the movement of the sun, wind, thunder, yea, even the murmuring of peristalsis was a manifestation of life within the abdomen. And when this murmuring was associated with illness, with purging and vomiting, why, surely something living was inside the abdomen, causing this disturbance. Thus the concept of a demon came into being. Unbeknown to our ancient colleague, however, it was a very modern concept. We call the demon a germ. With the passage of many centuries of miasmatic and ephemeral theories, we are again back to animism. Our demon is a microorganism—very much alive—and exorcised only with the greatest of difficulty.

What microorganisms, then, are responsible for diarrhea, and are they responsible for all cases of diarrhea? Here we are still on uncertain ground. Until about thirty years ago, the enormous influence of Finkelstein had established the cause of what he termed "decomposition" and "intestinal intoxication" to be due to a rather nebulous "metabolic breakdown" associated with heat and incorrect feeding. As late as 1928, Fischer,[2] author of a remarkably dogmatic textbook on pediatrics, laid down the law that it could be considered proved that bacteria played no part in the etiology of the disease, and that diarrhea was due to overfeeding, wrong feeding, and metabolic breakdown. Lest we smile at this, our attention must be drawn to the thesis of Dr. E. Kahn,[3] of Baragwanath non-European Hospital, Johannesburg, who wrote on "The Etiology Of Summer Diarrhoea" in 1952. While rejecting the bacterial etiology of ("nonspecific") summer diarrhea in the Bantu (on what appear to be quite *inadequate* grounds), he sums up his views as follows: "Summer Diarrhoea is a circulatory breakdown occurring in children who suffer from malnutrition. Heat . . . (per se) . . . precipitates this breakdown." Shades of Finkelstein! A few voices of partial protest were lifted against the influential pediatrician from Berlin. Griffith[4] (the original author of Mitchell-Nelson's textbook) notes in 1919: "Those who have long followed the increasing purification of the milk supply, as connected with the lessening morbidity and mortality of infants during hot weather, find it difficult to admit that bacteria play as small a part in the production of Summer Diarrhoea as Finkelstein's claims assign to them."[4] Hess,[5] while giving due regard to the concept of "metabolic breakdown" writes, "It is my belief, that in most cases there is an underlying infection of the gastro-intestinal tract. . . ."

A new appreciation is needed of Theodor Escherich (1857-1911) of Vienna, whose monumental labors on the bacteriology of the gut are a tribute to his industry and foresight. In 1927, Adam[6] recognized what he termed "dyspeptic coli," and in 1945 Bray[7] established a certain strain of *Escherichia coli* as being responsible for transmissible diarrhea. While it has been known for a long time that organisms such as Shigella, Salmonella, and Staphylococcus were capable of producing outbreaks of gastroenteritis, the incrimination of *Esch. coli* has been a real advance in pediatrics. Viruses have also been isolated and transmitted during epidemics of diarrhea.[8, 9] One can easily imagine that future studies may indicate that they play the principal role in the production of infantile gastroenteritis, but in the *meantime* the stage is held by the pathogenic Coli of Bray, since reported as being responsible for epidemics of gastroenteritis in many countries. In 1947 Kauffman[10] classified these pathogenic *Esch. coli* according to somatic ("O") and surface ("K" especially subtype "B") antigens. The commonest forms are 0.111B.4 and 0.55B.5, although at least eleven distinct pathogenic strains are known to exist. Carriers of these organisms have been found in parents and nurses. They have exceptional propensities for spreading through a ward, although, in so doing, they do not cause clinical disease in all or even in the majority of infants exposed. Probably at the age of a year most infants have already had subclinical pathogenic *Esch. coli* infections, and are immune in greater or lesser degree to reinfection. The incubation period is about 4 to 10 days, but can be as little as 24 hours. When disease does occur, clinical improvement runs reasonably parallel with the disappearance of these particular *Esch. coli* from the stool.[11]

It is becoming increasingly evident that these dyspeptic coli are pretty ubiquitous organisms, and are responsible for a great deal of the mild diarrhea in infants even in superior households. In this regard there is an especially significant report by Thomson and associates,[12] who summarize their work as follows: "Pathogenic varieties of *E. coli* were found in 1 per cent of faecal specimens from babies under one year old living at home. The infection rate was shown to be at least 25 per cent per annum. . . . Having regard for the technical difficulties and to the fact that specimens of faeces were examined only at fortnightly intervals, the suspicion arises that most, if not all babies are infected in the first year of life."

It is necessary to stress that gastroenteritis is a dangerous disease with a heavy mortality. In 1944 the *British Medical Journal* featured a paper[13] reporting on the treatment of 69 severely dehydrated infants, the resultant mortality being 11.6 per cent. The paper earned high editorial praise, since it was pointed out that the previous study on infantile gastroenteritis in 1941[14] had indicated a mortality of 53.7 per cent and that this figure was not unusual. Smellie[15] in 1939 reported a 48 per cent mortality, and Cooper[16] in 1937 a 47.2 per cent mortality. Alexander's[13] excellent results were largely due to the prompt and energetic use of intravenous plasma and Hartman's solution. Among the urban Bantu, gastroenteritis still has a heavy mortality despite what is by all standards good hospital treatment. At the Coronation non-European Hospital during the years 1948-1949, the mortality of gastroenteritis varied from 17 to 34 per cent[17]; Kahn[3] reported that in 446 cases treated in 1951 there were 204 deaths, a mortality of about 45 per cent, while Stein[18] at the same hospital recorded a mortality of 20 per cent in 170 infants with "nonspecific" diarrhea in 1954-1955. The conclusion seems inescapable that this high mortality in the hospitalized Bantu infants is somehow related to chronic undernutrition and liver disease, as well as to the fact that about a third of these infants are ill due to infections with Shigella and Salmonella organisms.

Contrary to convention, it is here found more convenient to deal first with the treatment of severe gastroenteritis, and later to consider the management of mild diarrhea. The treatment of severe diarrhea falls naturally into four categories: (1) medication; (2) intravenous therapy; (3) feeding; and (4) *Primum non nocere*—the prevention of potentially harmful procedures.

MEDICATION

"The Lord hath created medicines out of the earth and a wise man will not abhor them." Ben Sira 38:4.

From the very earth itself comes kaolin, hallowed by time and tradition. Used to give a deceptive bulk to the stool, it is still a favorite treatment for diarrhea, both alone and in combination with numerous other medicaments. Good evidence for its value is lacking, and the possibility at least exists that it may do harm because it absorbs water and electrolytes from the bowel. Apple, introduced by Moro[19] in 1929, has its advocates, and so has banana.[20] Bismuth and pectin are also extensively used, and carob flour (Arobon) has received support.[21] The *Lancet* recently featured a letter[22] extolling the properties of yoghurt in diarrhea. There is no really good evidence that these substances influence the course of a diarrhea, although by increasing the bulk of a stool they may cause a deceptive appearance of improvement. Their general use is falling into disfavor. Magnesium sulfate, castor oil, and opiates still have their occasional supporters, although it is certain that all three are dangerous for infants.

Chemotherapeutic substances are used in reasonable profusion and in various combinations as being effective in gastroenteritis.

Neomycin has been reported favorably[23] and at the present time is the only antibiotic against which *Esch. coli* has not yet developed resistance. Being poorly absorbed from the gastrointestinal tract, it may be given in large doses of 50 to 100 mg. per kilogram of body weight. Reports on other antibiotics are confused and probably depend principally on the sensitivity of the offending *Esch. coli* to the drug administered. Herweg and associates[24] use neomycin orally, at the same time giving penicillin and streptomycin parenterally to prevent complications. They feel that penicillin and streptomycin, as well as sulfonamides, are ineffective in diarrhea per se. Balnap and O'Donnel,[25] studying an outbreak of *Esch. coli* diarrhea, found that penicillin, streptomycin, Aureomycin, and Terramycin were ineffective but that the organism was sensitive to Chloromycetin, and that in this particular epidemic it was the drug of choice. They added the significant remark, "Recovery in the face of inadequate treatment seems to be dependent on the ability to form antibody." They also suggested that hyperimmune serum might be a useful adjuvant. They found that despite excellent biochemical stabilization some of their infants developed periodic episodes of collapse which responded temporarily to four-hourly administration of cortisone. Perhaps, like oxygen, it is nonspecific supportive therapy.

Also in the United States, Metzger and Jenkins[26] tested four strains of *Esch. coli* against various antibiotics in vitro. In terms of effectiveness, the order of the drugs was: neomycin, Chloromycetin, tetracycline, Terramycin, Aureomycin, and streptomycin—the last being very weak in its action. Neomycin, it was pointed out, was unlike the other broad-spectrum antibiotics in that it was actually bactericidal. They also noted that *Esch. coli* 0.127B.8 had the largest number of resistant strains.

In South Africa, the only report of significance is that of Stein[18] of Baragwanath non-European Hospital, who treated 170 infants with severe "nonspecific" gastroenteritis during the summer of 1954-1955. Divided into four groups, they were given either no chemotherapy, or else Terramycin, Chloromycetin, or a sulfa combination. Mortality and relapse rates were much the same in all four groups.

During 1950 to 1952 the British Medical Research Council (Dobbs and associates[27]) conducted clinical trials in ten different centers in England on the treatment of 1,168 infants with *Esch. coli* gastroenteritis (789 mild and 379 severe cases). Aureomycin and Chloromycetin, each in doses of 75 mg. per pound of body weight, and sulfadiazine in a dose of 125 mg. per pound were given for a week to respective groups. A control group received no chemotherapy. Three criteria were used to assess progress: (1) average duration of diarrhea; (2) average duration for full clinical recovery; (3) proportion of mild cases that became severe.

Aureomycin fared no better than the controls. The Chloromycetin group, compared to the controls, had a smaller proportion of infants progressing from mild to severe gastroenteritis, and the sulfadiazine group fared slightly better than any other treatment group.

On the basis of this report, Young and Rogers,[11] writing on the subject of recent advances in pediatrics, recommended the use of sulfadiazine in the treatment of severe diarrhea. As far as children are concerned, the poorly absorbed sulfonamides are probably of little value.

Perhaps a relevant report is the paper of Dubois,[28] who showed that in experimental animals a fast of 30 hours produced a demonstrable lowering of resistance to infection with the bacteria of tuberculosis, with Friedländer's bacillus and with staphylococci. It is common practice to partially starve infants with gastroenteritis, so that it is conceivable that their resistance to complications may be lowered, thus heightening the necessity for chemotherapeutic cover.

INTRAVENOUS THERAPY

"The tongue of the sucking child cleaveth to the roof of his mouth for thirst." Lam. 4:4.

Nineteen centuries passed before Jeremiah's description of the effects of dehydration was again recognized by O'Shaughnessy of Newcastle in 1831. In that year he wrote a short letter to the *Lancet* describing the changes in the blood in cholera.[20] Since then, many advances in pediatrics have come, not from clinicians, but from biochemists. There has been a tendency of late, certainly in the United States, to appoint biochemists or physiologists to chairs of pediatrics—a procedure which has a great deal in its favor. Ever since Marriott took over the chair of pediatrics at St. Louis in 1917, numbers of biochemists have entered via a side door, as it were, to become prominent in the field of pediatrics. A hundred years ago, Pasteur wrote of the increasing value of the laboratory in medicine: "Take interest, I implore you, in those sacred dwellings which one designates by the expressive term laboratories. Demand that they be multiplied, that they be adorned. These are the temples of the future, temples of well-being and of happiness. There it is that humanity grows greater, stronger, better." Today, nobody can practice good pediatrics without the aid of the laboratory, and certainly, the future will see increasing use made of this valuable service.

To return to dehydration: A year after O'Shaughnessy's letter, Thomas Latta of Leith, Scotland, again wrote to the *Lancet*[29] describing the case of an old woman dying from cholera, whom he temporarily revived from a moribund state by the use of an intravenous salt solution. In the same epidemic he managed to save eight out of sixteen moribund individuals with the intravenous use of a solution containing ±0.4 per cent sodium chloride and ±0.3 per cent sodium bicarbonate —approximately isotonic. His work was buried beneath a welter of medical opposition, and in 1892 Cantani of Naples redescribed the intravenous treatment of cholera in a Berlin journal.[29] Thereafter, from time to time, despite much opposition, some intrepid individuals dared to experiment with fluids and salines subcutaneously, intraperitoneally, and even intravenously. In the latter half of the nineteenth century, a number of biochemists (Schmidt, von Bunge) performed important studies on the biochemistry of the blood, and, in 1916, Howland and Marriott[30] of Baltimore made the discovery of the acidosis of severe diarrhea. In the early 1900's Finkelstein's use of the unfortunate term "decomposition" delayed for some years the recognition that in gastroenteritis the operative feature was not decomposition but desiccation. This was demonstrated by Marriott in 1920.[31, 32] It then took some twenty years for intravenous therapy really to take root, and the next significant advance was the demonstration by Govan and Darrow[33] in 1946 of the important role played by potassium in intravenous medication.

In the same year (1892) that Cantani of Naples rediscovered the use of intravenous saline, Cheadle[34] of the Westminster Hospital re-emphasized the desiccation resultant from severe gastroenteritis: "The incessant draining off of food, and *especially of liquid,* by the incessant vomiting and purging, causes the child's tissues to shrink." But he did not follow this thought to its logical conclusion. By 1915, Still[35] mentioned the use of subcutaneous saline, as did Griffith[4] in 1919. In 1922 Hill[36] noted Marriott's work on dehydration and was in favor of giving fluids by mouth, subcutaneously, intraperitoneally, and even intravenously. A year later, Brennemann[37] stated: "Latterly we are hearing much about anhydraemia as the important factor in the severe intoxications with diarrhoea and vomiting." In 1916 Morse[38] of Boston almost gave intravenous therapy pride of place.

Improvements in the manufacture of intravenous apparatus permitted the development of a high degree of skill in the technique of intravenous infusions. The use of the Gardner-Murphy needle[39] and of scalp veins has much to recommend it. Regarding "cut-downs" at the ankle, it is necessary to draw attention to a common fault of inexperienced operators in making a half-inch incision rather high above the ankle. The best incision is placed just at the distal anterior end of the internal malleolus and need not be more than about ⅛ inch long. The vein can be picked up with a minimum of dissection, and after a nick has been made in the wall, a cannula (size 1 polythene is suitable for infants) is threaded up the vein for a few inches and the ankle is tightly strapped with tape; if desired it may be fixed to a splint. In infants it is wiser to use a splint because acute flexion at the knee tends to obstruct the flow in the long saphenous vein. It is unnecessary to tie any portion of the vein with catgut or to use suture for the skin.

The ensuing discussion concerns itself only with intravenous infusions. Although subcutaneous infusions are often helpful, they have their limitations and hazards, as do also intraosseous and intraperitoneal infusions. Sagittal sinus infusions are little more than a historical curiosity. The decision to set up a drip is a clinical one. ("The best time to set up an intravenous infusion is when one begins to wonder if it will be necessary.") While whole blood and plasma are useful in the initial treatment of severe gastroenteritis, most cases can be adequately treated by means of various saline solutions. It is customary to calculate the intravenous necessity on a basis of a 24-hour requirement, and for severe gastroenteritis an easy scheme to remember is that a 5 pound infant needs 500 ml. over 24 hours at

5 drops per minute; a 10 pound infant needs 1,000 ml. at 10 drops per minute; and a 15 pound infant needs 1,500 ml. at 15 drops per minute.

If, as many believe, an infant with severe gastroenteritis should be totally starved for 24 hours or more, then this scheme for 24-hour fluid requirement is reasonable. Otherwise it has its defects. An infant with diarrhea and vomiting cannot have plans made for him 24 hours in advance. When he has passed two or three watery movements, the calculated 24-hour requirements become totally inadequate. Balnap and O'Donnel[25] state of their cases of severe diarrhea: "Day after day the fluid requirements seldom dropped below 300 cc/Kilo/day" (that is, twice the accepted 24-hour requirement). It is not at all uncommon for an infant to get the theoretical 24-hour requirement in 6 to 8 hours and thereafter remain fully hydrated purely on oral intake. While calculations based on the 24-hour fluid requirement are helpful in a general way, it is preferable to reasses the requirements on the basis of clinical observation at intervals of a few hours, on the response to oral intake, and on the features of repeated laboratory studies. As a general scheme, provided there are no rapid fluctuations in the clinical condition, the basic 24-hour requirements for parenteral alimentation in infants are:

1. Fluid, 150 ml. per kilogram body weight per day.
2. Sodium and chloride, each 6 to 8 mEq. per kilogram per day.
3. Potassium, 2 to 3 mEq. per kilogram per day.
4. Calories, 50 per pound (if possible).
5. Vitamins and calcium, q.s.
6. T.L.C. (tender loving care), q.s.

The scheme is not as helpful as it appears. The situation is analogous to that of food requirements. While we may specify that an infant needs certain basic requirements of calories, fluid, protein, fat, carbohydrate, vitamins, and minerals, yet we may sidetrack the difficulties involved by stating that all these requirements are met by sufficient quantities of the substance known as milk. In the same way, it may be stated that a number of intravenous solutions adequately meet many of the intravenous requirements of infants, without going into advanced mathematical calculations regarding their contents.

In calculating requirements for the three principal electrolytes, a distinction must be drawn between potassium, on the one hand, and sodium and chloride on the other. Potassium is largely an intracellular ion, a very tiny proportion of it being in the interstitial fluid and plasma. Thus the plasma value of potassium can hardly be expected to portray the intracellular state, though, in general, a low plasma value indicates a low intracellular concentration. (The reverse is not true!) Intravenous potassium may thus be given in concentrations larger than that of the plasma (normally about 5 mEq. per liter), and in general 2 to 3 mEq. per kilogram per 24 hours will meet basic potassium requirements, though much more will have to be given if there is continuing loss via the bowel. Laboratory studies and the electrocardiogram are of considerable benefit in this regard.

In the matter of sodium and chloride necessities, we are on easier ground. Aside from the sodium deposits in the bones, most of the sodium chloride is contained in the extracellular fluid, and the plasma concentration of these ions therefore gives an accurate representation of their concentration in the interstitial fluid. When calculating sodium and chloride deficiencies, one must also take into account this interstitial fluid. In older children, its volume is about 3 times the plasma volume, and in infants perhaps 4 to 5 times that of the plasma volume. Now plasma volume is calculated on the basis of 25 ml. per pound of body weight (blood volume is 40 ml. per pound) so that total extracellular (i.e., plasma plus interstitial fluid) fluid volume is perhaps 100 to 150 ml. per pound, and sodium chloride requirements must be calculated on this basis, though it must be admitted that if oral intake is adequate, intravenous needs will be correspondingly less.

To reiterate: Those ions which are largely intracellular, such as K, PO_4, and Mg, may be given intravenously in concentrations exceeding that of the normal plasma values, but as regards sodium and chloride, these must be given in concentrations equal to or preferably lower than the normal plasma values of sodium and chloride (about 140 and 100 mEq. per liter, respectively). Normal saline, it must be remembered, is only normal as regards the red cells. In respect of the plasma it is abnormal saline. Its concentration of ion (154 mEq. of Na and of Cl) is in excess of that in the plasma. Like the Holy Roman Empire, which was neither holy nor Roman nor an empire, normal physiological isotonic saline is neither normal, nor physiological, nor isotonic from the point of view of clinical therapeutics.[40]

It should also be remembered that, in an occasional case of diarrhea, hyperpnea due to metabolic acidosis plus perspiration consequent on pyrexia combine with stool water loss and sodium chloride retention due to immature kidney function to cause an excessive water loss relative to ionic loss, thus producing a state of hypertonic dehydration, for which a dilute ionic solution is necessary as intravenous therapy. Theoretically one would imagine that in such a case one should administer a solution free of sodium chloride (such as 5 per cent dextrose water), but this practice often results in the development of convulsions thought to be due to "water intoxication" at high levels of sodium chloride concentration.[41] Also, when vomiting is excessive, alkalosis may result from the gross loss of chloride ion, and this may be dealt with by giving a fluid with a high concentration of chloride.

It has been considered that a primary necessity of intravenous treatment was the correction of a low carbon dioxide value. Formulas were evolved with this in view, and M/6 lactate solutions were given according to various schemes in order that the lactate might be metabolized to bicarbonate. It was noted that 2 ml. per pound (4 ml. per kilogram) of M/6 lactate raised the plasma carbon dioxide 1 mEq. per liter, and on a clinical basis the average infant needed perhaps 15 to 20 ml. per kilogram of lactate. Today there is no longer such emphasis on the carbon dioxide. If prompt attention is paid to correcting the sodium, chloride, and potassium losses, the bicarbonate will look after itself.

The problem now arises: What is the most suitable solution for initial use in the rehydration of infants with severe gastroenteritis? In view of the possibility of potassium intoxication (a concentration of 8 to 10 mEq. per liter may be fatal) it is considered wise by many not to give this ion until the kidneys are functioning, so that solutions of NaCl alone are suitable for initial rehydration. Talbot[42] in 1953 advised, "Such solutions (½ to ⅔ saline with dextrose) appear suitable for the initial hydration of most severely sick patients. However, these solutions are inadequate for prolonged treatment because they lack ions essential for repair of intra-cellular deficits (K, PO_4)."

It is possible, however, that the hazards of initial potassium use have been overrated. A small bottle of 150 ml. of Darrow's solution—which contains a total of about 5 mEq. K—is often suitable for initial use, though one-half strength Darrow's might be preferable. Ringer's lactate is also suitable for initial rehydration, though after a few hundred milliliters it will be necessary to add extra potassium. Butler's solution does not have this defect. It is also satisfactory for initial use. So is 0.2 per cent NaCl in 5 per cent invert (a similar solution is popular in England: ⅕ saline in 4.3 per cent dextrose) which may be followed up with Darrow's solution. Amigen solution is eminently satisfactory both for initial rehydration as well as continuing treatment. It not only contains protein and carbohydrate, but also valuable electrolyte concentrations, including phosphate, magnesium, and calcium, a lack of the latter sometimes becoming clinically evident during the recovery stage of gastroenteritis. If one considers the requirements of an infant of 5 kilograms (11 pounds), it will be clear that the daily requirement of water will be in the region of a liter, and the sodium and chloride requirements (each about 6 mEq. per kilogram per 24 hours) about 30 mEq. of each daily, and the potassium need (about 3 mEq. per kilogram per 24 hours) about 15 mEq. daily. These almost exact quantities of electrolyte are in fact contained in a liter of Amigen solution, so that for an infant of perhaps 9 to 12 pounds, a liter of Amigen would be admirable for supplying the basic daily water and electrolyte needs as well as some very necessary protein and calories. In most instances, however, it would be necessary to add molar lactate solution to the Amigen solution because not only basic daily requirements must be supplied, but also the continuing stool and vomitus losses must be corrected, and sodium is the principal ion affected in these losses. Travamin, a protein preparation with an allegedly higher nitrogen availability, is not as satisfactory as Amigen in that it has no dextrose added to it, and no electrolyte.

Table I illustrates the principal ionic concentrations of a number of materials.

Finally, one must stress again that one cannot make too elaborate calculations too far in advance. The situation is rather analogous to diabetic coma. One can have a general idea of the insulin requirements over the next 24 hours, but for good care it is necessary to have frequent blood sugar estimations. Nor can severe gastroenteritis be satisfactorily treated without frequent clinical reassessment and laboratory aid. In this respect the increasing availability of microchemical estimations will render valuable

TABLE I. MILLIEQUIVALENT CONCENTRATIONS OF VARIOUS SUBSTANCES

	Na	Cl	K	HCO_3	Ca	Mg	PHOSPHATE
Plasma	142	103	5	27	5	3	
Darrow's solution	120	103	35	53			
Butler's solution	55	45	23	26		5	12
Ringer's lactate	130	109	4	28	3		
0.2 per cent NaCl (with dextrose)	34	34					
Amigen solution	30	22	15		5	2	30
Cow's milk	27	33	40		60	10	54
Diarrheal stool	55	40	40				

service. Herein the plea of Pasteur has special appeal. Still needed from the laboratory are simple methods of estimating total intracellular and extracellular water content.

Notwithstanding the value of the laboratory in clinical pediatrics, however, it must also be stressed that the body has remarkable powers of adjustment and recuperation, provided it is supplied with the necessary material so that it can repair the ravages of disease and dehydration. Provided one supplies basic water and ionic requirements in reasonable quantity, the homeostatic mechanisms of the body will be well capable of restoring metabolic normalcy.[43]

FEEDING

"Milk is a substance midway between food and blood." Koran 16:68.

This section concerns itself almost entirely with boiled cow's milk and its role in the feeding of infants with diarrhea. I believe that there is no other field in pediatrics in which an understanding of present practices and tendencies is so dependent on a knowledge of what has gone before, as is the subject of the feeding of infants in health and in sickness. How many mothers know, indeed how many doctors know, that when an infant is given diluted feeds the massive influence of Adalbert Czerny is extending its effects over a half-century of pediatric thought?

Czerny advanced the theory that at times various constituents of the milk could prove poisonous for the infant, especially in producing diarrhea. His favorite target was the fat, and an immense clinical edifice was built around "fat dyspepsia." While at various times the claims of protein, sugar, and even electrolyte dyspepsia were pressed (yet never the quite valid water intoxication!), the concept of fat intolerance survived, and is very much alive even today. The reading of some standard works on the alleged menace of fat is a source of some interest, if not amusement. What better samples of clinical obfuscation could be found than the following authoritative extracts?

This from the pen of Joseph Brennemann[37]: ". . . Cow's milk fat causes two wholly opposed disturbances, di arrhoea and constipation . . . fat indigestion can manifest itself as diarrhoea. . . . on the other hand . . . fat when given in excess (leads to) constipation. . . . There is no more constant symptom of fat intolerance . . . than vomiting." Morse,[38] in his book of 1926, also notes that fat may cause both diarrhea and constipation. In 1929, Cautley and Paterson, writing in Thursfield and Paterson's work,[44] note that "excess of fat may set up 'fat constipation,' 'fat dyspepsia' or 'fat diarrhoea.'" More recently, Paterson and Newns,[45] in their rather conventional work, remark on page 113 that excess of fat in the diet results in diarrhea, whereas on page 70 they aver that it results in constipation. As if the confusion for doctors is not enough, the same privileges are extended in 1950 to the poor harassed mother by the Ministry of Health and Welfare of Ottawa[46]: "If fat is at fault," the booklet notes, "it causes constipated stools containing soft fatty nodules which will float in water. After a time the child may develop diarrhoea, and vomiting is common." This is clinical fence sitting in its most highly developed form.

The belief that something in the milk engendered cholera infantum naturally suggested that, in its treatment, the milk should be withheld and only reintroduced with caution and in considerable dilution. This is the basis of the conventional oral treatment of diarrhea today. In general, the foundation of such therapy is that the infant should be starved for some 12 to 48 hours (some authorities suggest even longer[47]) and during this period, while on intravenous fluids, he should either get nothing at all by mouth (in order to "rest the bowel") or else clear fluids of various kinds. Thereafter milk was to be carefully reintroduced in considerable dilution, working up to the full formula by the fourth to tenth day. Should the diarrhea recur, then temporary redilution of the formula was again necessary. Full-cream milk was taboo. Various modifications were advised, especially half-cream milks, lactic acid milks, and protein milk. In addition, sugar was commonly restricted also and perhaps saccharin was given in its stead, due to the influence of Finkelstein's views on sugar dyspepsia. Subject to minor variations, these views have been propounded by such authoritative works as those by Rotch,[48] Moose,[38] Hess,[5] Hutchison,[49] Jeans and Marriott,[50] Brennemann,[51] Parsons and Barling,[52] Sheldon,[53] Slobody,[54] Paterson and Newns,[45] Paterson and Lightwood.[55] They have also been recommended to the public at large in various popular medical works such as that of Spock[56] and in *The Complete Book of Mothercraft*.[57] Moncrieff and Evans,[58] Holt and MacIntosh,[59] and Nelson[60] also mention this as *a* method of treatment, but do not pronounce it *the* method.

The necessity for restricting milk in diarrhea was not only advised but, in the past, was insisted upon with some vehemence. Miller, writing in an authoritative textbook[44] in 1929, remarks, "Milk acts as a veritable poison and must be absolutely withheld. All are agreed on that point." Fischer[2] in 1928 is equally insistent and emphasizes the point by heading a chapter on "Food Intoxications" with the subheading of "Acute Milk Infections." He also shows a photograph of a malnourished and dehydrated baby with the caption of "a case of acute milk poisoning." Even Griffith[4] (the first "Mitchell-Nelson") has a paragraph on "Acute Milk Poisoning." Still[35] prohibits milk in any shape or form, and the venerable Eustace Smith[61] wrote as early as 1884 that, in "choleraic diarrhoea," "milk in any shape, even breast milk, must be strictly forbidden."

Notwithstanding the views of Paterson and Newns[45] on the treatment of nonspecific diarrhea by means of partial starvation, they express opposite views on the treatment of the specific diarrhea of typhoid fever: "Typhoid patients require a high caloric intake if wasting and loss of strength are to be avoided. . . . Greater errors are made in underfeeding than in overfeeding in this disease." As long ago as 1912, Du Bois[62] showed that in typhoid, digestion and assimilation were seldom more than 10 per cent below the normal. Jeans and Marriott[50] in 1947, while advocating conventional views on partial starvation in nonspecific diarrhea, express opposite views on the treatment of the specific diarrhea of bacillary dysentery: ". . . Starvation, even if prolonged, is likely to have but little effect in causing a cessation of the diarrhoea." Many of those who earnestly advocate restricted feeding in diarrhea, at the same time warn against this very practice. Cheadle[34] writes as early as 1892: ". . . Do not commit the common, fatal error of putting the child on mere barley water . . . except for a short time at first. This may agree, but it is starvation diet." Brennemann[37] also writes: "The case of barley water deserves a special consideration. Barley water has become a sort of national institution in this country. When a baby has a diarrhoea, its milk is discontinued and barley water is given alone for a day, unfortunately only too often for many days . . . whether in very young infants it may not at times rather keep up than lessen a diarrhoea is at least an open question." Similar sentiments have been expressed recently by Vining[63]: "It has often amused me to watch doctors awaiting the return of an infant's stools to normal while a baby is being given quantities of glucose solution, or a weakened feed which could not possibly produce a normal stool." Jeans and Mariott[50] and also Hess[5] advise against prolonged underfeeding, the latter noting, "It is . . . dangerous to inaugurate starvation repeatedly. . . ." In this regard, one may consider as significant the report of Du Bois,[28] who demonstrated a lowering of resistance to bacterial infection in experimental animals following a fast of 30 hours. In this regard also, one may note as a disturbing feature the tendency of some drug companies to put electrolyte solutions on the market for oral use. While they have their value as adjuncts to intravenous treatment in severe diarrhea, their use in mild diarrhea must be viewed with some misgivings, especially if they are given instead of milk, rather than as an adjunct to milk. It appears that these electrolyte solutions may become a fruitful source of iatrogenic starvation, as did barley water some twenty or thirty years ago.

Relapse of diarrhea is also considered to merit the necessity of reintroduction of a starvation regime. We have already noted that Hess,[5] while agreeing to a starvation regime in diarrhea, nevertheless warns against repeated starvation. Watkins and Paterson,[52] writing in the textbook edited by Parsons and Barling, advise that "should the diarrhoea continue the feed may need further dilution. . . ." Mann and asociates,[64] in analyzing 286 cases of diarrhea, remark: "The relapses, although a well-known feature of the disease, may in some of our cases, have been due to a too rapid stepping up in the quantity and quality of oral feeds." Taking an opposite view are Chung and Holt,[65] who wrote in 1950: "It has been our impression for some time past that true relapse in diarrhoeal states was due to the vagaries of the disease, being unrelated to the oral food load." Balnap and O'Donnel[25] describing their experiences with gastroenteritis in 1956 write: "The numerous relapses of severe diarrhoea were independent of the oral fluid and electrolyte replacement schedule."

Earlier it was noted that fat was believed potentially inimical to healthy infants—hence how much more so was it to be feared for infants who already had diarrhea. But evidence has been accumulating that fat is not especially harmful to infants, either in health or in sickness. The recent trend is to question the alleged malign influence of cow's milk fat. As regards digestibility and assimilability it does not differ significantly from the fat of breast milk.[51] The view that a high fat diet per se can lead to fat intolerance does not bear critical analysis.[59] Even the casein of cow's milk is not especially inferior to the lactalbumin in respect to essential amino acids.[66] Hytten and MacQueen,[67] who fed exceptionally high caloric intakes to infants, failed to produce any digestive disturbances or associated illnesses; and in the treatment of diarrhea, Lanman[68] doubts that the use of skimmed or lactic acid milk has a demonstrable superiority over evaporated milk. In his book to mothers, Goldbloom[69] writes a courageous account of the treatment of diarrhea. He inveighs against the use of barley water, and although he does not state that normal milk feedings can be continued, equally he does not advise that they must cease forthwith. He writes: "After the acute stage of diarrhoea has subsided, it can be unnecessarily prolonged by a diet too poor in fat. Skimmed milk is often fed in the early stages of diarrhoea. Its prolonged continuance may cause a persistence of looseness which will stop overnight when some cream is added back in the milk."

Such thoughts are turning points in our ideas on feeding during diarrhea, and indicate that in this sphere of treatment, evolution is taking place. In 1949, Mitchell[70] reported on 396 cases of gastroenteritis in 70 per cent of which full-strength skimmed milk was given within 8 to 24 hours after admission. In comparing their results with those of other series, they considered such early feeding advantageous. Chung[71] and Chung and Viscorova[72] took the final step. They gave early feedings of full-cream milk to infants with gastroenteritis and compared the results with a control series fed in the conventional manner. In general, those infants on early full feeding, despite the resultant increase in stool volume, did better in all respects than infants treated by means of partial starvation. Balance studies indicated that "... even in the severest cases increased intake resulted in increased assimilation of every nutrient studied."[73, 74] This statement is illustrated in Table II.

Chung and Holt[65] remarked: "Diarrhoeal deaths, when they occur, are almost entirely restricted to severely malnourished infants. It was this observation which inspired our efforts to improve nutrition in this condition by early oral feeding." Gomez[76] emphasizes the relevant point that "... the fear of losing other nutrients, especially some minerals, by increasing the intake of foodstuffs in general, and of fat in particular, does not seem to be justified." Further related work

TABLE II. LOW ORAL INTAKE (24 Cal. Per Kilogram) AND HIGH INTAKE (100 Cal. Per Kilogram) (First and Second Columns, Respectively) IN TREATMENT OF GASTROENTERITIS

	ORAL INTAKE		FECAL LOSS		ABSORBED		PER CENT INTAKE ABSORBED	
Water (ml./day)	960	1,410	156	270	804	1,140	84	81
Fat (Gm./day)	7.35	29.4	3.42	12.1	+3.93	+17.3	53	59
Nitrogen (Gm./day)	1.15	4.6	0.46	0.5	+0.69	+4.1	60	88
Na (mEq./day)	5.6	22.4	7.2	18.1	-1.6	+4.3	-	19
K (mEq./day)	8.3	33.2	9.4	12.3	-1.1	+20.9	-	63
Ca (mEq./day)	12.8	51.2	20.8	42.7	-8.0	+8.5	-	17
Cl (mEq./day)	6.8	27.2	12.0	21.6	-5.2	+5.6	-	27

(From Holt, L. E., Jr.: Arch. Dis. Child. 31: 427, 1956.)

in early full feeding has been performed also by other workers.[65, 75-78]

It would thus appear that the main principles for the feeding of an infant with diarrhea are the same as those for the feeding of an infant without diarrhea. The fact that there is an inflammation of the digestive tract is irrelevant. Karelitz,[79] while using conventional feeding in diarrhea, states, however: "It has been our experience that . . . the type of formula does not seem to be very significant."

Young and Rogers,[11] in writing a 17 page account in 1954 on recent advances in gastroenteritis, hardly mention the subject of feeding, and other recent papers on diarrhea either disregard it or deal with it as a rather unimportant afterthought.[24, 25, 80] It is interesting that up to the time of World War II, a paper on the treatment of gastroenteritis might have concerned itself almost wholly with the matter of feeding, whereas now the question of feeding barely merits mention. So it seems that the skill involved in managing the feeding in diarrhea differs in no whit from that of managing the feeding of healthy infants. It involves not an ability to change the constituents of a diet, but the ability to manage the practical and mechanical difficulties which may be associated with feeding. This statement needs one qualification, however, applicable not only to the use of full-cream milk in gastroenteritis but also to the use of any milk. Aspiration of vomited milk is a common terminal event in infants who have been exhausted by severe gastroenteritis; therefore, if vomiting has once occurred, it is wise to give clear fluids until it is reasonably certain that vomiting will not recur. This, in fact, is the reason for stopping milk in the presence of vomiting in infants severely ill from whatever cause. Despite a widespread impression, there is no evidence that clear fluids per se are less emetogenic than milk in the presence of a propensity to vomit such as occurs in gastroenteritis.

PRIMUM NON NOCERE

"Spake I not unto you, saying, Do not sin against the child?" Gen. 42:22.

The following letter to the editor, from a practitioner in Natal, appeared in the *South African Medical Journal,* Jan. 19, 1957,[81] dealing with the subject of the treatment of diarrhea: "This simple treatment, which has proved very successful, consists of the frequent giving of fractional doses of $MgSO_4$. . . . I obtained such good results . . . that it was introduced into all . . . wards as a routine procedure in all cases of infantile gastro-enteritis. Fractional doses of, say, 2-5 gr. of $MgSO_4$ are given every 1, 2 or 4 hours, according to the age and condition of the patient. Whereas a large dose of $MgSO_4$ is aperient in its action, in very small doses it acts as an astringent. When necessary, other better known treatments were combined with the giving of $MgSO_4$, such as a preliminary dose of castor oil, the withholding of food, and the giving of much plain water by mouth, together with saline infusions when required. Intestinal lavage, in severe cases, was also helpful. The results were almost universally successful, except in cases that were too advanced when admitted. . . ." The operative phrase here is certainly the last one. Analysis of his advice reveals that every single item mentioned, unless further qualified, is likely to do damage to the infant. Magnesium sulfate will further deplete the body reserves of fluid and electrolyte. So will castor oil. The withholding of food and the giving of water only is unwise; at least if fluid is to be given, it should contain electrolyte and calories. Saline infusions must not be normal saline. Intestinal lavage is at least a means of supplying fluid, though care must be taken that the fluid given contains reasonabble quantities of electrolyte, for water intoxication is also to be feared; or alternatively, if, as is not uncommon, 2 to 3 per cent sodium bicarbonate is used, hypertonic dehydration may result.

Castor oil had a great vogue in the early days and was enthusiastically advised by many authorities such as Morse,[38] Griffith,[4] Fischer,[2] Miller,[44] and Pritchard,[82] who wrote: "In all cases of acute diarrhoea, from whatsoever cause arising, the first essential is to clear the bowel of its irritating contents. A moderate sized dose of castor oil is the best means of securing this end." Truby King,[83] being much preoccupied with stools, also advised castor oil. He agreed with the dictum that "the first question in almost every disease in children should be, 'What are the motions like?' " Certainly stool gazing as a guide to treatment is also an overrated pastime.

In fairness, it must be stated that some people were opposed to the cult of castor oil. Jeans and Marriott[50] considered it inadvisable, and as early as 1917 Grulee[84] totally opposed it. Still[35] in 1915 advised small doses of castor oil for its alleged constipating effects.

Other remedies are opium, favored by Eric Pritchard,[82] and surviving to this day in the form of Chlorodyne. Miller[44] in 1929 also advised opiates as well as brandy. At least the latter is a source of some calories. One still sees brandy and sal volatile prescribed where intravenous fluids are clearly the prime necessity.

Kaolin, bismuth, pectin, charcoal, apple, banana, yoghurt, and Arobon are of questionable value. One need hardly mention that infusions into the sagittal sinus must be wholly proscribed, and that intraosseous and intraperitoneal infusions are not without danger.

At one time, surgery, especially of the mastoid, had great vogue in infantile gastroenteritis. The place of surgery in this disease is well illustrated by the discussion from the floor that took place in 1936 during a meeting of the Hunterian society. One speaker, deploring the high mortality of 70 per cent, suggested exploring all possible avenues with a view to improving on this deplorable state of affairs. "Could not the surgeon do something?" he pleaded. Another voice from the floor interjected, "He could make it 80 per cent!"[85]

In the light of what has been mentioned, we may now reasonably discuss the treatment of mild diarrhea. Holt[59] states that it should be entirely expectant. Moncrieff and Evans[58] advise that fluids only should be given for 24 hours. Young and Rogers,[11] on the basis of the British Medical Research Council trials in 1952,[27] feel that chemotherapy should not be employed in view of the fact that 62 per cent of untreated patients recovered in up to 10 days merely on temporary starvation. Though I also feel that the treatment should be entirely expectant, in private practice one has to deal with the sensitivities of anxious parents, and thus one may be prompted to prescribe medicaments such as kaolin, or to advise temporary dilution feeds. The mothers expect it. On occasion one may even feel inclined to administer a sulfa preparation (the poorly absorbed sulfas have no special virtues), but my own feeling is that, unless one gives an antibiotic to which the infecting organism is especially sensitive, it is as difficult to influence the course of a "running tummy," as of a running nose. The only medicament that definitely helps is a little tincture of time.

Expectant treatment, it must be understood, does not mean doing nothing. It also entails repeated clinical observations of the infant, the prevention of noxious influences, and the curbing of distracted relatives who insist on "doing something." It means also that the child is not to have his food stopped and be fobbed off with a fancy electrolyte solution, or even with the relatively old-fashioned glucose or barley water—the latter fluid still being advised by many popular medical works read by the laity, such as, for example, the 1957 edition of *The "Lactogen" Mother Book.*[86]

Finally, to emphasize the fact that the practice of the past shows us the road to the future, we can do no better than to quote from Forsyth,[87] an English pediatrician of the early 1900's: "Our 20th century methods, be it understood, are not of 20th century make. They are covered with the fingernails of old-time gossips and dented with the prejudices of half a dozen centuries. If history told us nothing more than this it would still teach us that today we are watching a passing stage of a developing subject. It should, however, do more than this; by tracing the route we have already travelled it points the direction toward which we are moving."

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Comments on Current Literature

ASEPTIC MENINGITIS DUE TO STRAINS OF ECHO VIRUS

ACCURATE etiologic differentiation of the aseptic meningitides is assuming greater importance, especially since vaccines for protection against poliomyelitis have come into general use. In a number of institutions conscious attempts are being made at the present time to evaluate the prophylactic efficacy of formalized poliomyelitis vaccine based on results obtained from virologic studies of patients. Such experience over the past several years in the Toronto area has been reviewed recently by Rhodes, Beale, and their associates.[1, 2] In one series, ". . . virus studies suggested that the etiology of 96 cases of aseptic meningitis ('nonparalytic poliomyelitis') was as follows: poliomyelitis, 19 per cent; Coxsackie B infection, 24 per cent; Echo virus infection, 11 per cent."[2] One group studied in detail comprised twenty-seven children, ranging in age from 5 to 12 years, who were admitted to a pediatric hospital during the summer and fall season with the diagnosis of "poliomyelitis." Thirteen of the twenty-seven children had been vaccinated with formalized poliomyelitis vaccine the spring previous to the admission. One child of the thirteen who had been vaccinated experienced a paralytic illness, and twelve of the thirteen vaccinated children, a nonparalytic illness. The authors state that "none excreted poliomyelitis virus, but four isolations of Echo viruses, and one of Coxsackie B virus were made."[2] Exact etiologic diagnosis was not accomplished in the eight other vaccinated children. Fourteen unvaccinated children of this group of twenty-seven were admitted to the hospital with the possible diagnosis of nonparalytic polio. In one of these the tentative diagnosis was supported by the isolation of poliovirus, type 1. From the stool specimens of nine of the fourteen Echo viruses were recovered. Another group studied in detail consisted of thirteen unvaccinated children in whom the clinical manifestations apparently left less doubt as to the diagnosis. From twelve of these thirteen paralyzed patients, strains of poliovirus were obtained readily by tissue culture methods.

Poliomyelitis-like illnesses characterized by meningeal signs or muscular weakness or both seem to have been occurring recently in epidemic form. In a surprising number of these recent "epidemics" strains of Echo virus have been incriminated. The Echo viruses (enteric, cytopathogenic human orphan viruses), of which about eighteen antigenically distinct types are known, were first isolated as an incidental finding, being obtained by tissue culture from fecal specimens of healthy children. They were called orphan viruses because their classification was not apparent immediately and because their pathogenicity for human subjects was undetermined. Until recently their relation to human disease was a matter of conjecture. Since in some of the earlier studies strains of Echo virus were recovered with considerable regularity from stool specimens of apparently healthy children, they were regarded by many as possible normal constituents of the human enteric flora. Several strains seem to have been associated with diarrheal conditions in early childhood, particularly types 2, 8, and 13. While this virus group may consist in general of nonpathogenic strains (the so-called "viruses in search of disease," or viruses "orphan" with respect to human disease[3]), there can be little doubt in the light of recent developments that some strains have been incriminated in aseptic meningitis, particularly types 6 and 9. Type 4 also has been added recently.[4] Evidence of the association of these enteric viruses with human disease is strong where the laboratory findings have included isolation of the strain from cerebrospinal fluid specimens obtained during the course of clinical illness.[5, 6]

During the summer of 1955, and again in the midsummer season of 1956, outbreaks of aseptic meningitis occurred in various parts of the world, notably in the United States and Canada and in parts of Western Europe: Belgium, the Netherlands, Germany, Switzerland, Denmark, and England. One of the earlier epidemics in England centered in the region of Nottingham, which led to the use of the term "Nottingham meningitis," especially in the lay press. At the same time, outbreaks were occurring in other parts of England, with the result that information was disseminated, comparative studies were made, and "Nottingham meningitis," like the other cases of aseptic meningitis being encountered, was attributed to infection with a viral agent identified as Echo, type 9. This strain of Echo virus was isolated readily from throat washings, from stool specimens, and in a remarkable number of instances from cerebrospinal fluid.[5] Appropriate serologic studies substantiated the virus isolations. Of the epidemics in Western Europe, those in Belgium and the Netherlands have been described in recent publications.[6] From a total of 399 patients showing the characteristic clinical manifestations, 225 virus isolations were made: 190 from fecal specimens, 29 from cerebrospinal fluid, and six from throat swabs. In the case of some of the patients the increase in neutralizing and complement-fixing antibodies during the course of clinical recovery was as much as fourfold. The clinical manifestations described in the various epidemics are somewhat variable. Predominant features recorded, however, were fever, nausea and vomiting, frontal headache and photophobia, signs of meningeal irritation, pain in the neck and shoulders, transient muscular weakness, and in about 25 per cent of the cases, largely children, a macular rash, often rubelliform in type.

Outbreaks in the United States have been recognized for the past several years. At a symposium held in New York City in April, 1957, entitled "Viruses in Search of Disease," Enders and his associates[7] reported the isolation of Echo virus, type 6, from 40 patients whose illness occurred in the late summer or early autumn of 1954. In all of these patients with aseptic meningitis the initial diagnosis by the attending physician had been that of nonparalytic poliomyelitis. During the same period strains of poliovirus were isolated from only sixteen patients. In all forty of the patients with evidence of Echo virus infection muscle weakness of a mild or moderate degree was a consistent finding. Periodic muscle examinations were possible in 37 of the 40 patients at from 10 to 20 days and from 50 to 70 days after onset. In most instances this weakness disappeared within a reasonable period of time. At the same conference in New York City, Meyer and his colleagues[8] described aseptic meningitis occurring among United States military personnel. In a group of 416 cases studied between 1953 and 1956, specimens from thirteen of the patients yielded Echo viruses, eleven of which were type 6.

Other outbreaks in the United States include those in Connecticut and New York State[9] in the summer and fall of 1955, due largely to Echo virus, type 6. An epidemic of such poliolike illness, which occurred in western New

York in the summer of 1955, was considered atypical for poliomyelitis, since a large proportion of the cases was nonparalytic. Epidemiologic, clinical, and laboratory studies were undertaken by a group of virologists and epidemiologists, Winkelstein, Karzon, Barron, and Hayner,[10] with results published in the *American Journal of Public Health*, June, 1957. From 68 per cent of 156 patients, studied during and immediately following the epidemic, Echo virus type 6 was recovered; polioviruses were recovered from 4 per cent of these patients, and other cytopathogenic agents from 6 per cent. Of eleven successful isolations from cerebrospinal fluid, the agent recovered in eight was Echo, type 6. During the epidemic, household or other close contacts of patients were included in the study. Persons under the age of 20 years who were in close (household) contact with patients had a high incidence of minor illness—36 per cent; more than one-half of these contact persons (55 per cent) were shown to be infected with Echo virus, type 6.[10]

An investigation conducted about the same time, which concerned an epidemic in Marshall County, Iowa,[4] is of special interest in that the Echo strain isolated consistently was type 4. Successful isolations included recovery of virus from fecal specimens and from the oropharynx. In addition to the study of clinical cases, a survey was made of the community for the incidence of minor illnesses. Virus isolations from apparently healthy contacts and from family members with minor illnesses, correlated with antibody studies in these contacts, revealed "a broad spectrum of illness," since Echo virus, type 4, was incriminated not only in cases of aseptic meningitis, but seemed to account for the considerable incidence of minor illness prevalent at the time. Recovery of this strain from apparently healthy individuals indicated the presence in the community of asymptomatic cases or of entirely silent infections in the population at large.

Reports in recent issues of the *Canadian Medical Association Journal*[11] describe further outbreaks of Echo type 9 meningoencephalitis in Canada, in which the patients, largely children, experienced the rubelliform rash, reported previously, and marked muscle weakness as a part of the clinical syndrome. In one locality seven cases of aseptic meningitis occurred in a single family of eight members. These seven patients ranged in age from 24 years down to 3 months. Muscle pain and tenderness were quite apparent in all of these patients and, in some of the older children, spasm of the hamstrings was marked. In the Toronto area over 100 children were admitted to the Hospital for Sick Children with a diagnosis of aseptic meningitis. Enquiries from practitioners indicated that many cases were occurring at the same time throughout the city and were being cared for at home. Similar illness had been noted in some adults. Examination of spinal fluid specimens revealed pleocytosis with counts as high as 2,000 cells per cubic millimeter. An interesting feature was the high neutrophil count, especially in the early stages of the disease. Virus isolation was attempted from 94 fecal specimens and from 48 samples of cerebrospinal fluid. Fifty-eight strains of Echo type 9 virus were recovered from fecal specimens, and fifteen strains of virus from samples of cerebrospinal fluid. All of these agents proved to be cytopathogenic in tissue culture preparations, and in none of the agents isolated could the cytopathogenic effect be neutralized by antisera to poliomyelitis viruses, types 1, 2, or 3.

During the summer of 1957 two epidemics of aseptic meningitis in the United States received considerable publicity in the lay press, one in Milwaukee, and one fanning out from the twin cities of Minneapolis and St. Paul. From time to time, information was relayed to the medical profession by way of the medical news weeklies. Laboratories participating in the investigation of these epidemics, which were of sizable proportions, included those of Dr. Albert Sabin of Cincinnati and Dr. Frederick C. Robbins of Cleveland. Echo virus, type 9, was cultured from specimens of spinal fluid and of fecal material. Maculopapular rash was a common finding, especially prominent over the abdomen and flexor surfaces of the arms. Laboratory findings were not consistent with the diagnosis of nonparalytic poliomyelitis. Spinal fluid cell counts were high, ranging from 300 to 2,400 cells; spinal fluid protein was essentially normal. The epidemics seem to have reached a peak in August. One of the major problems was the high infectivity of the disease during the long incubation period of from one to two weeks.

The consistent finding of the rubelliform rash in this type of aseptic meningitis recalls the occurrence during the past several years, especially in the eastern part of the United States, of an unusual type of exanthematous disease. The clinical manifestations resemble erythema infectiosum, or fifth disease, described previously. From its prevalence in Boston in 1951 the disease was called "Boston exanthem."[12] Outbreaks of this disease occurring in Pennsylvania in 1954 and 1955 have been reported recently.[13] Strains of virus, isolated readily from fecal specimens, less readily from nose and throat washings, and in one instance from blood, seem identical with, or closely related to, strains isolated in cases of Boston exanthem.[14] Complete identification of the strains has not been accomplished as yet. It has been suggested that this exanthematous disease might be a manifestation of infection with one of the types of Echo virus.[7, 14] Of the known strains of Echo viruses, types 4, 6, and 9 seem to have been incriminated definitely in the etiology of aseptic meningitis. At the Fourth International Poliomyelitis Conference in Geneva in July, 1957, considerable discussion centered around the prophylactic efficacy of available vaccines against poliomyelitis and the basic principles underlying active immunization. The recent publications summarized here indicate that clinical manifestations simulating poliomyelitis can be due to the Echo group of viruses, as well as to those of the Coxsackie group. The occurrence of infections of this type will need to be considered in any evaluation of the efficacy of polio vaccines.

Russell J. Blattner

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News and Notes

At a dinner at the Hotel Pierre honoring *Dr. Béla Schick,* world-famous pediatrician, on his 80th anniversary, the governing council of the **Collegium Internationale Allergologicum** conferred upon Dr. Schick the first honorary fellowship in this medical organization.

The Collegium Internationale Allergologicum, founded in 1953, consists of 80 members from 18 different countries. Fellowship is by invitation only; no country may have more than 12 active fellows; and only those doctors and medical scientists who have made unusually important scientific contributions to allergy and allied fields may become fellows.

A Festschrift or birthday volume to honor Dr. Schick on the occasion of his 80th anniversary is being prepared for publication in the spring as a special issue of the *International Archives of Allergy and Applied Immunology.* Leading medical teachers, scientists, and physicians from the United States and foreign countries are contributing scientific papers on various aspects of allergy and immunology. Dr. William Kaufman will edit this volume which will be published by S. Karger of Basel, Switzerland, and New York.

At the dinner, Dr. Rene Dubos of the Rockefeller Institute for Medical Research presented Dr. Schick with the Annual Award for Service to Mankind given by the Business and Professional Associates of the American Jewish Congress.

The University of Oklahoma School of Medicine announces the first Oklahoma Colloquy on Advances in Medicine, on Feb. 6, 7, and 8, 1958. It will be devoted to problems on Fluid, Electrolyte and Nutritional Balance. Nine nationally prominent investigators will participate and present the results of original work from their laboratories. The list of guest speakers is as follows: William E. Abbott, M.D., Cleveland, Ohio, Curtis Artz, M.D., Jackson, Miss., John H. Bland, M.D., Burlington, Vt., Robert E. Cooke, M.D., Baltimore, Md., Ben I. Heller, M.D., Little Rock, Ark., Rachmiel Levine, M.D., Chicago, Ill., John F. Mueller, M.D., Cincinnati, Ohio, Arnold S. Relman, M.D., Boston, Mass., and Robert Tarail, M.D., Buffalo, N. Y.

The College of Physicians and Surgeons Columbia University announces a three weeks' *Postgraduate Course in Cerebral Palsy* for physicians, March 3 to 21, 1958. This course is designed (1) to acquaint potential leaders in this field with the basic knowledge concerning cerebral palsy; (2) to review the present status of practical therapy, including the medical, social, educational and psychological aspects; and (3) to point out the controversial features of our present understanding. Detailed information can be obtained from the Dean, College of Physicians and Surgeons, 630 West 168 Street, New York 32, N. Y.

The Twelfth Annual Symposium on Fundamental Cancer Research at **The University of Texas M. D. Anderson Hospital and Tumor Institute,** Houston, Texas, will be held March 6-8, 1958.

The **Fifth International Congress of Internal Medicine** will be held at Philadelphia, April 23-26, 1958. This is the first meeting of the Congress in the United States. Dr. T. Grier Miller of Philadelphia is President of the Congress.

The **Third Congress of the International Diabetes Federation** will be held in Düsseldorf, Germany, July 21 to 25, 1958. In addition to the scientific program, social-medical subjects will be discussed by the diabetic organizations affiliated with the Federation. The Congress is held in collaboration with the German Diabetes Association. Prof. Dr. M. Bürger, Leipzig, Prof. Dr. E. Grafe, Garmisch-Partenkirchen, and Prof. Dr. G. Katsch, Greifswald, are Honorary Presidents, and Prof. Dr. K. Oberdisse, Düsseldorf, is the Chairman of the Congress; Privatdozent Dr. K. Jahnke is the scientific head of the organizing office. The address of the "Organisationsbüro" is II. Medizinische Klinik der Medizinischen Akademie, Düsseldorf, Moorenstr. 5. The languages used at the Congress will be German, English, and French.

Dr. P. Schwenger, Düsseldorf, Humboldtstr. 57, is the President of the German Diabetes Association.

Drs. Elliot P. Joslin, of Boston, and Dr. Charles H. Best of Toronto are the Honorary Presidents of the International Association, and Dr. R. D. Lawrence of England is President and Chairman of the Executive Board.

A new nonprofit foundation, the **National Tay-Sachs Association, Inc., New York Chapter,** has been established to support and stimulate research, clinical and educational programs in Tay-Sachs' disease and allied heredofamilial, neurodegenerative diseases of infancy and childhood. The scope of the program will include, in addition to Tay-Sachs' disease, Niemann-Pick's disease, infantile Gaucher's disease, Schilder's disease, diffuse sclerosis, amyotonia congenita, Friedreich's ataxia, and others. The operation of the foundation is on a nationwide basis, and contact is being made for establishment of chapters in other metropolitan areas, in addition to the allied Tay-Sachs Association in Philadelphia. In order to further its work and, in particular, to prepare a substantial genetic study covering the entire country, physicians and hospitals are respectfully requested to make the existence of the foundation known to parents of children afflicted with these diseases.

For further information on the foundation and its work, write to Medical Committee, National Tay-Sachs Association, Inc., New York Chapter, P. O. Box 1250, G. P. O., New York 1, N. Y.

Two films on **Schizophrenia in Children** are now available and may be rented by writing to the League for Emotionally Disturbed Children, 10 West 65th Street, New York 23, N. Y. These films were taken at special schools for schizophrenic children and show the lack of responsiveness, compulsive behavior, and bizarre gestures of these children. Each is about 15 or 20 minutes long. They were shown by Dr. Ruth Bakwin at the American Academy of Pediatrics meetings in 1956. There is a charge of $5.00 for the silent film and $7.50 for the sound film to cover handling, postage, insurance, etc. Anything extra is a contribution to the L E D C. For your convenience in arranging a showing of either film, it is requested that the following form be used.

To the L E D C Film Department
10 West 65th Street
New York 23, New York

I would like to rent the 16 mm film "Schizophrenia in Children."
On Preferred Date Alternate Date
Sound Silent
Name (please print)
Address
City Zone State
Name of group to which it will be shown (this must be professional or scientific—not parent groups).
Your request will be acknowledged. Please give four weeks' notice whenever possible.

The **American Cancer Society** has announced that **Clinical Fellowships** at the senior resident level for the academic year 1959-1960 may be applied for by institutions accredited by the Council on Medical Education and Hospitals of the American Medical Association to give training in the following specialties and subspecialties, with emphasis on the diagnosis and treatment of cancer: internal medicine, malignant diseases, neurological surgery, obstetrics-gynecology, orthopedic surgery, otolaryngology, pathology, public health, radiology, surgery, and urology. Institutions will be notified of awards granted in June, 1958. Individual candidates should apply directly to an institution, or the

American Cancer Society, for information concerning fellowships. The annual stipend, tax exempt, is $3,600.

Application forms are available from the Director of Professional Education, American Cancer Society, Inc., 521 West 57th Street, New York 19, New York. Feb. 15, 1958, is the deadline for institutions submitting applications for the 1959-1960 clinical fellowships.

Applications are now being received for three- to six-month *residencies in Pediatric Rehabilitation* at the **Jewish Chronic Disease Hospital,** Brooklyn, New York. Residents are given an opportunity to gain experience in the rehabilitation approach to the chronic diseases of children, including: the neuromuscular diseases such as poliomyelitis, spina bifida, muscular dystrophy; visceral handicaps such as congenital heart disease and cleft palate; and a variety of communication and psychologic handicaps. The service is a teaching unit of the State of New York Medical School and is fully staffed and fully equipped for this type of work. There will also be experience in cardiac catheterization, angiocardiography, and an opportunity to observe patients undergoing cardiological operations. The stipend is $175 a month. Applicants receiving their pediatric training in an accredited institution will receive 3 months of credit toward certification by the American Board of Pediatrics. Vacancies are now open beginning July 1, 1958. Applications should be sent to Director of Pediatrics, East 49th Street & Rutland Road, Brooklyn 3, N. Y.

A fellowship in *renal research* will be available beginning July 1, 1958, in the **Department of Pediatrics, Western Reserve University School of Medicine.** The candidate would be expected to spend approximately two-thirds of his time in laborartory research and one-third in clinical work with patients under investigation. Salary will be $4,500 to $5,000. Applicants with minimum training of two years in Pediatrics preferred. Direct correspondence to Walter Heymann, M.D., 2103 Adelbert Road, Cleveland 6, Ohio.

Third-Year Residency in *Pediatric Specialties,* **St. Christopher's Hospital for Children, Department of Pediatrics, Temple University School of Medicine,** a special residency providing longitudinal experiences in several of the subspecialties of pediatrics throughout the year, is available to candidates who have had an internship and two years of pediatric residency. The resident may participate in the planning of his program. One or more days of each week may be spent in such specialties as cardiology, neurology, hematology, endocrinology, allergy, and psychiatry. This program has been devised as a pilot study for the training of pediatricians to fill the gap now existing between the general practitioner type of pediatrician and the one highly skilled in a given specialty. It is thought that pediatricians with such additional training should (1) improve materially the quality of general pediatric practice, (2) serve more adequately as consultant with the general practitioner, and (3) work effectively with the larger pediatric centers in the care of children who for one reason or another must receive a part of their medical care in such centers.

Appointments will be made for residencies beginning on July 1, 1958 about March 1, 1958. For applications write to: Waldo E. Nelson, M.D., St. Christopher's Hospital for Children, 2600 N. Lawrence Street, Philadelphia 33, Pa.

The **Childrens Hospital of Los Angeles** announces a residency in *Pediatric Hematology* for one year beginning July, 1958. The resident in hematology participates in all phases of diagnosis and management of clinic hematology patients. He serves as consultant to the pediatric house staff and participates in hematology teaching rounds. Opportunity is also available to learn various hematology laboratory procedures and to participate in research related to hematology. The resident in hematology has customarily completed two years of acceptable training in pediatrics and desires further experience and training in pediatric hematology. There is a stipend of $275 per month. Interested applicants should write to: Phillip Sturgeon, M.D., Head, Hematology Research Laboratories, The Childrens Hospital of Los Angeles, 4570 Sunset Boulevard, Los Angeles 27, Calif.

Books

Mental Deficiency, in Relation to Problems of Genesis, Social and Occupational Consequences, Utilization, Control and Prevention. Wallace J. E. Wallin, Brandon, Vt., 1956, Journal of Clinical Psychology, 200 pages. Price $5.00.

Drawing from his lifelong experience and intensive review of the literature in the field of mental deficiency, Dr. Wallin presents evidence pro and con on major social problems, dealing with the control and training of mental defectives.

Throughout his discussion, Dr. Wallin emphasizes the community's responsibility for developing resources and programs to train mental defectives and to keep them out of trouble, stressing the fact that the mentally retarded person is primarily a victim of his environment, and that he can be an asset or a liability, depending upon the development of resources within the community.

Discussed at great length are the major issues of institutionalization versus sterilization, methods of prevention of propagation, special schools, classes and training programs, residential colonies, and home placement. The abundance of footnotes, references, and bibliographies to substantiate the author's points of discussion are especially commendable and are indicative of his thoroughness as a research person.

Summaries at the end of each chapter formulate specific conclusions as to possible solutions to the many problems presented by mental deficiency in the community. Hereditary aspects, the social consequences, and preventive aspects of deficiency are also covered at great length. Dr. Wallin, who describes this book as a "sort of digest of basic problems still in need of satisfactory solution," has long been known as one of the most capable and productive authorities in the field of mental deficiency. His viewpoints are especially valuable because a large part of his professional career has been spent working in communities throughout the nation where he has had a remarkable opportunity to become familiar with all of the practical problems integrating retardates to community schooling, working, and living. This book is a fine contribution to the field of mental deficiency, and a definite asset to physicians, psychologists, teachers, social workers, and community planners.

F. A. B.

International Congress of Gastroenterology —Fifth Meeting of L'Association des Sociétés Européennes et Mediteranées de Gastro-Enterologie, London, July 18-21, 1956.

This compendium of the papers given during the 1956 International Congress of Gastroenterology is concerned for the most part with diseases of the esophagus and ulcerative colitis. A section of short papers covers a wide variety of gastrointestinal subjects with the emphasis on hepatic disease and peptic ulcer.

In the section on diseases of the esophagus, the ingenious methods devised to study esophageal physiology are especially noteworthy, and serve to confirm present ideas concerning normal activity of this organ. Peptic esophagitis and achalasia are well covered under disease conditions. The diverse experiences in diagnosis and treatment of ulcerative colitis in many parts of the world are worth reading as a commentary on management of this baffling disease. Hepatic coma in England, an interesting concept of infantile cirrhosis with unknown etiology in Indian children, and several papers on precursors of gastric cancer are of special interest in the miscellaneous group.

Many of the individual publications may be recommended on their own merits, and the over-all view afforded the reader of gastrointestinal conditions in other parts of the world is well worth the time spent in browsing through this manuscript.

R. S. N.

The Doctor Eyes the Poor Reader. Delwyn G. Schubert, M.S., Ph.D., Springfield, Ill., 1957, Charles C Thomas, 101 pages. Price $3.75.

This is an unusual and interesting discussion of reading difficulties, written for the physician. The author, Professor of Education and Director of the Reading Clinic at the Los Angles State College of Applied Arts, has no particular theory or cause to try and put across as has been the case in so many of the recent discussions of dyslexia, but approaches the subject in a broad way. His theme is that as reading difficulties may be due to a number of causes, and many of these are physical, the doctor is in a position to discover them and give advice as to their remedy. The cause may be the result of some type of visual defect, auditory defect, poor intelligence, or a general health problem. The various tests to be used in discovering the cause of the reading difficulty are presented in a simple direct way. One gathers he is not impressed with the overwhelming importance which has been given to laterality as a cause nor does he consider the method of teaching reading in the schools as the chief cause of reading troubles. The book then considers the ways by which the poor reader may be helped. It is a book or discussion that will interest the pediatrician.

A Visit to the Hospital. Produced and Issued by the Health Centre for Children, The Vancouver General Hospital, Vancouver, B. C.

This is one of the more clever of the booklets that have been published in the last few years with the purpose of preparing young children for hospitalization. This particular booklet is designed for children of the preschool-age period. It consists of sixteen pages carrying the story in simple rhyme. What makes it of value is that each page contains excellent outline drawings of the story, to be colored in crayon by the child. Thus the authors have utilized one of the proved and accepted methods of amusing young children and holding their interest. Physicians considering the use of such booklets would do well to consider it. It has a definite age limitation.

The Story of Peptic Ulcer. Richard D. Tonkin, M.D., F.R.C.P., with illustrations by Raymond K. Hellier, F.R.S.A., Philadelphia, 1957, W. B. Saunders Co., 71 pages. Price $2.25.

While this little book, with the subtitle "Dawn for Depressed and Disappointed Dyspeptics," written for the laity, does not concern a disease of much interest to the pediatrician—unless he happens to be a ''victim of the villain,'' it is so well done and the drawings are so clever that every physician will enjoy it. There have been other attempts to present information in a similar way, but none that we recall have done it so well.

The Good Housekeeping Book of Baby and Child Care. L. Emmett Holt, Jr., M.D., New York, 1957, Appleton-Century-Crofts, Inc., 288 pages. Price $4.95.

The remarkable progress that has taken place in pediatrics and in infant and child care is brought out strikingly in this text by Holt Jr., when one compares it with the pioneer book in the same field by Holt Sr., published in 1895. Customs and methods have undergone great changes over this span of years. It is, of course, another text in a field and for the same purpose that a number of excellent books are available. It is well written, sound, and in keeping with present-day knowledge and thinking. While the format is good, a larger font of type would have made it easier to read. A number of the illustrations are without point or value. The book may be classed as one of the better of the many published for the same purpose.

Hepatitis Frontiers, Proceedings of an International Symposium sponsored by the Henry Ford Hospital, Detroit, October, 1956. Boston, 1957, Little, Brown & Co., 595 pages. Price $12.50.

Forty-one papers presented at the Symposium, including the discussions, have been collected in this volume. The papers are grouped into six sections: Anatomy and Physiology of the Liver; Virology and Epidemiology; Prevention—Blood Donor and Storage Problems; Prevention—Chemical and Physical Agents; Differential Diagnosis including Laboratory Methods; Clinical Management. Leading scientists from ten countries participated in the symposium. The volume is of fundamental importance and value to those who are interested in, or working on, any of the aspects of this unconquered viral disease. The very nature of the Symposium and the breadth of its scope make a detailed review of the contents impossible. It has been unusually well edited.

Editor's Column

CLINICAL-PATHOLOGIC STUDIES AS A METHOD OF RESEARCH

RECENT advances in many phases of medicine, e.g., in the knowledge of intermediary metabolism, in the use of radioactive isotopes, and in the application of new radiologic techniques, have led many to the erroneous conclusion that research must of necessity be conducted in large medical centers and must utilize complicated, expensive equipment. The importance of careful observation, meticulous recording of facts, and correlation of the findings so recorded are often overlooked as an essential tool to medical progress. Hadley, Gault, and Graham, in the article "A Study of Pathology of Stillbirths and Neonatal Deaths in South India" which appears in this issue of the JOURNAL (p. 139) clearly demonstrate an important type of research which is conducted by means of careful observations and by correlation of clinical and pathologic findings. The advances which may result from such a technique, although often not as impressive as those associated with more dynamic studies, have formed in the past and will continue to form one of the essential bases for medical progress.

Although the definition of the neonatal period employed by these authors is admittedly at some variance with that commonly employed, the bulk of the "neonatal" deaths (up to 3 months of age) occurred during the first 28 days after delivery. The results of the investigations reported might, therefore, justifiably be compared with those reported from this country.

There are, indeed, striking similarities as well as a few noteworthy differences between the causes of death as given by these authors and as recorded from this country. As in any series of carefully conducted postmortem examinations, the authors note the difficulty in establishing a primary cause of death. Even with the most detailed clinical pathologic correlation, only an arbitrary decision as to the primary cause of death can be made in many instances, and the multiplicity of lesions encountered by the pathologist may render interpretation as difficult in some infants as does the paucity of lesions in others.

The role played by prematurity as a cause of death in this series cannot be assessed from the data given. Although 29 of the total of 215 deaths are attributed to prematurity alone, the authors are obviously cognizant of the inadequacy of this as a sole diagnosis. The importance of racial and/or dietary and economic factors in establishing a definition of prematurity are again emphasized, the weight of the normal full-term infant in the Christian Medical College Hospital (6 1/4 pounds) being more than 1 pound less than the average weight of the full-term infant in this country.

The importance of infection, especially of pneumonia, as a cause of neonatal death is emphasized by the authors. Since usually only one or two sections of lung were examined, the authors' statement that the actual incidence of pneumonia was probably higher than that recorded is undoubtedly correct. With rare exceptions, the diagnosis of pneumonia in infants dying in the early neonatal period must be made by histologic studies and not by macroscopic examination. Nevertheless, 20 per cent of the infants died as a result of pneumonia, and in almost 10 per cent of the remaining infants pneumonia was present as a contributory cause of death. In many instances the inflammatory process appeared to have arisen in utero. Although the agents responsible for pneumonia were not identified bacteriologically, the authors' description of a necrotizing pneumonia with the presence of basophilic amorphous debris suggests that Gram-negative bacilli may have played an important role in many instances. The incidence of infections encountered by these authors may exceed that reported from some areas in the United States, but it is, nevertheless, becoming increasingly apparent that even the liberal use of antimicrobial agents in the newborn nursery has not eradicated infections as a cause of neonatal death.

The paucity of pulmonary hyaline membranes as a cause of death in this series of infants is of particular interest. Oxygen was administered to the one premature infant who died with pulmonary hyaline membranes, but information as to the frequency with which this was given to other premature infants is not available. Clinical records suggest that oxygen is not the sole factor responsible for pulmonary hyaline membranes in newborn infants, but there are now a number of indications to suggest that it may play a role in the development of such membranes.

The authors are to be congratulated on the care with which they have conducted this study, and it is to be hoped that their work may serve as a stimulus to others to carry out comparable research. Periodic evaluation of the causes of neonatal death is essential to the prevention of such deaths. The frequency of certain pathologic lesions in one geographic area as compared with another, when correlated with the different factors acting in each region (e.g., environment and methods of therapy), may lead to important conclusions with respect to the etiology and pathogenesis of these lesions. As a result, a better understanding of the factors responsible for certain pathologic lesions may be forthcoming, with a resultant over-all improvement in neonatal mortality rates.

James B. Arey, M.D.

THE MANAGEMENT OF GASTROENTERITIS

IN THIS issue (page 227) we publish an interesting and rather unusual historical review by Levin, of South Africa, of the many changes that have taken place in the theories and practices in regard to the management of gastroenteritis in infancy. Some of this is familiar to the older pediatricians who lived through the years when the management of gastroenteritis was the subject of active controversy. We realize that a few of the author's statements and opinions will not be acceptable to some of our readers. Perhaps the most important consideration about the condition, its almost complete disappearance in some countries such as the United States as a result of preventive measures, is not a part of the author's theme. That a few cubic centimeters of prevention, to paraphrase an old saying, is better than barrels of electrolyte fluids is strikingly illustrated by the history of the incidence of gastroenteritis in infancy.

"OMNIUM GATHERUMS"

SOME months ago, as an aftermath of attending the International Congress of Pediatrics in Copenhagen in 1956, as well as some of our own recent American pediatric meetings, the question was raised editorially in the JOURNAL as to whether the value of the meetings was decreasing as their size increased.

Our attention was recently called to an article by Professor Witts, Nuffield Professor of Clinical Medicine at Oxford, who related in the *Lancet* (June 22, 1957) his thoughts and reflections on medical travel occasioned by a lecture tour to Australia and the Far East. He incidentally discussed these *omnium gatherums,* as he so aptly terms them.

"One thinks of the long period of gestation, the delay between the acceptance of a paper and its delivery, which means that the material is already out of date by the time it is given; the concessions to international susceptibilities in the choice of programme; the ageing stage-army of regular performers; the frequently deplorable level of presentation; the devitalised version of the addresses that comes over the Tannoy; the impossibility of discussion; the host of papers read by title so that participants can obtain currency allowances and tax reliefs; the inability to see one's friends unless one arranges a rendezvous beforehand; the banquets with the conventional references to the internationality of science; the expensive outings and the crowded sightseeing—and one wonders sadly whether medicine, too, has not come under the sway of Admass.

"Congresses have become too large and too frequent if their object is the advancement of medicine and the promotion of friendship among physicians. The cost per head rises steeply when the attendance exceeds a few hundred, and the organisers become preoccupied with the physical problems of the meetings, the organization of entertainments and the collection of subventions from the pharmaceutical and other industries."

Our own comments reflected conversations with a number of pediatric leaders from a number of countries. Obviously there is concern in the minds of leaders in other branches of medicine as to the value of these *omnium gatherums.* What a splendid descriptive term!

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SUVREN IN BRAIN-INJURED CHILDREN

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A CHILD'S brain may be damaged by a variety of factors before birth, during the birth process, or in early postnatal life. The results of such damage may affect any of the major functions of the brain, singly or in combination. The major functional spheres affected are: *motor function* (in that case, the term "cerebral palsy" is frequently used); *reasoning and learning ability* (in these children, the term "mental retardation" is applicable); the *special senses* (mainly hearing and vision); *action and behavior;* and the *presence of seizures.*

In this report, we are mainly interested in children whose actions and behavior are significantly different from those of others, presumably because of organic brain damage. In addition to the changes in personality and behavior, they may or may not have various forms of cerebral palsy, may or may not be retarded, have visual or auditory disturbances, or be subject to seizures. As a group, these children are characterized by emotional instability, lack of inhibition, impulsive actions, restlessness, and general hyperactivity.[1 (a)] They are "erratic, uncoordinated, uncontrolled, uninhibited, and socially unaccepted."[1 (b)] The concept of the psychopathology, as well as testing and educational techniques, has been formulated by Strauss and his collaborators.[1, 2]

Chemotherapy.—Attempts to affect these overactive children favorably with medication have in general been unrewarding. The barbiturates usually are not helpful; in fact, they frequently aggravate the restlessness and lack of inhibition. Amphetamine, strangely enough, has been found effective in some cases.[3-5]

Tranquilizing medicines have therapeutic value not only in emotional problems of children[6] but also in brain-injured children, regardless of the level of intelligence or the presence or absence of seizures. Tranquilizers, like chlorpromazine, Rauwolfia compounds, and meprobamate,[4, 5, 7] seem to increase the attention span and facilitate management. Unfortunately, the percentage of beneficial responses is not high and the results are not constant. Nevertheless, the recent advances in the chemotherapy of diseases of the psyche and the central nervous system offer the hope that drugs more effective

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in the treatment of brain-damaged children will be forthcoming. We have been on the alert to determine the possible efficacy of new drugs in this field, especially those with purported different modes of action and pharmacologic effects. One of these drugs that came to our attention was Suvren (captodiamine)* which we feel merits reporting because of the potential it has shown.

Pharmacology.—Noting the sedative effect of diphenhydramine, Weidmann and Petersen[8] altered the molecule to develop and enhance this property. Among the 35 chemicals tested in animals, para-butyl-mercaptobenzhydryl-beta-dimethyl-aminoethyl sulfide hydrochloride (captodiamine) was selected for clinical evaluation because it effected significant sedation without hypnosis, had the least toxicity, and possessed as well musculotropic spasmolytic properties.[9] Because of these pharmacologic effects Suvren seemed to us suitable for clinical investigation in brain-injured children. Furthermore, Bakwin and Bakwin[10] have reported that diphenhydramine itself can be a "valuable therapeutic aid" in the treatment of these patients.

Several papers on its clinical action[11-17] have been published, and others are in press or in preparation.[18, 19] These reports deal primarily with neurotic and psychotic adults. Besides sedation, investigators have observed a mild stimulating action on depressed and melancholic patients[17] and a "loosening up" or antirepressant effect in schizophrenics.[20]

Clientele.—The 40 children treated were outpatients of the Department of Pediatrics of the University of Utah at the Salt Lake County General Hospital (private and clinic), the Children's Health Center of the Utah State Health Department, and inpatients at the Utah State Training School. All met the criteria of Strauss[1] of "brain-injured" and fit into the syndrome recently described by Laufer and Denhoff,[4] Milman,[21] and Bender.[22] The patients varied in age from 2 to 40 years; all but 5 were under 15. There were 23 males and 17 females.

Method.—Forty patients were given Suvren in an attempt to make them more manageable and to decrease their impulsive actions, restlessness, and hyperactivity. Children under 6 years were usually started on 50 mg. twice per day; older patients, three times per day. In many instances it was necessary to increase the dosage to 250 mg. daily to get the desired effect. Almost all children receive 250 mg. at this time. Higher dosages were not used in this group but should be tried in future studies. No attempt at running controls with placebos was made.

Results.—Patients were classified as having a "positive" response when there was a striking improvement in their behavior, when they could be more easily controlled, and their attention span was prolonged. In some of these children the value of the medication was clearly demonstrated by relapses when therapy was temporarily interrupted. The response to Suvren was called "negative" when the desired improvement did not occur or was equivocal. The evaluation was based on reports by parents, teachers, institutional attendants, and physical therapists as well as those of the authors. Twenty-three patients had a positive response; 17 showed no or questionable improvement. There did not appear to be any correlation between response and age or sex. Improvement was usually evident within 2 to 5 days on an adequate dosage. Children who did not respond favorably were maintained on Suvren for from 2 weeks to 3 months before being classified as negative and the medication was then discontinued. Some patients have been treated for months with no signs of becoming tolerant or refractory to the medication.

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*Kindly supplied by Dr. Louis Parrish, Ayerst Laboratories, New York City. Marketed in Europe as "Covatin."

Of the 23 children who had a positive response, 7 had been tried unsuccessfully on one to five other tranquilizers before Suvren was started. In the remaining 16 patients it was the first medication offered. Seven of the children in the negative group had been tried on one to four different tranquilizers or amphetamines with poor results before Suvren was given.

The following case history typifies the patient who had a positive response:

S. W., a 3-year-old girl, had congenital right spastic hemiplegia, a history of three convulsions, and slight mental retardation. The seizures had been controlled with Dilantin, 150 mg., and phenobarbital, 50 mg. daily. (This was continued during the Suvren study.) Physical therapy had been prescribed but could not be carried out because the child would run around the room wildly, turn over, throw around loose objects, and disturb other children in the program. Her attention span was too short to permit her to sit still for passive exercises or to listen to instruction. In the doctor's office on each visit she would throw herself on the floor or try to open the door while screaming.

One week after receiving 150 mg. of Suvren daily, she elected to sit on the examiner's lap, was quiet and affectionate, and cooperated with the therapist. The mother is now able to do her housework and enjoy her home life without having to watch and restrain her daughter continuously. The child falls asleep without struggle soon after being put to bed but does not sleep more hours than before. She is alert and active on awaking in the morning.

Toxicity and Side Effects.—Suvren to date has not been demonstrated to be toxic or to produce significant untoward side effects. Complete blood counts and urinalyses have been done in most cases while the patients were receiving Suvren. A slight or moderate increase in the total leukocyte count without apparent infection was found on one or more occasions in 3 children, and one child had 7 and 8 per cent eosinophils, respectively, on two examinations. No explanation for these mild changes is known, and they may not be related to the administration of the drug. No abnormal urinary findings were noted.

Two brothers whom we attempted to include in this series could not be started on Suvren because they refused to swallow the coated pills, which taste bitter when chewed. One other boy who is not counted in this report vomited each time he took the medication. Lethargy, undue sleepiness, and grogginess were not encountered. No patient developed ataxia, nystagmus, or other neurologic findings while on Suvren; nor was there any evidence that previously present abnormal neurological signs were ameliorated. There was no indication that Suvren affected seizures either favorably or unfavorably. No rashes or other forms of sensitization were noted, even in the children who received interrupted treatment.

DISCUSSION

The results reported here indicate that Suvren is a useful medication in the symptomatic treatment of overactive, brain-injured children. In the series of 40 patients, 23 children who were inattentive, hyperactive, and destructive became amenable to management and instruction. In many of these the response was dramatic, especially in those who had failed to respond to all previous chemotherapy.

The reason for Suvren's efficacy in these patients is not clear. Its reported combination of sedative, stimulating, and "loosening up" effects may provide an explanation. It is impossible to say at this time why Suvren was effective in some cases and not in others. Perhaps, in the future, more specific recommendations as to the selection of cases can be made.

It is true that this effect of stabilization, when achieved, does not solve all problems, but the reduction of hyperactivity and increase in attention span eases the physical and emotional burden on the family or attendants. We do not think that Suvren, tranquilizers, or amphetamines truly increase the I.Q., but amelioration of symptoms often makes the patient more amenable to constructive play and formal education.

A principal advantage of Suvren seems to be its safety, especially the absense of a hypnotic effect. The useful response is not due to sedation and drowsiness but to the reduction in overactivity per se without apparent depression and without affecting the mental alertness of the patient. Because the medical and social problems of brain-injured children are so great and Suvren appears so promising in the easing of their difficulties, we have presented our experience and want to encourage other investigators to use this medication in the same syndrome.

SUMMARY

Forty hyperkinetic children with patterns of organic brain damage were treated with a new type of "mental drug," Suvren. Dosage varied from 100 to 250 mg. daily for periods of 3 to 17 months. Twenty-three patients showed striking improvement in action and behavior.

No significant toxic reactions or untoward side effects were demonstrated.

Our results indicate that Suvren is a safe and useful chemotherapeutic agent in the treatment of hyperactive children with brain damage.

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Could It Have Been the Asiatic Variety?

Epidemic Diphtheric Angina at Lima.—About the close of the month of July, 1851, an epidemic grippe appeared, and suddenly attacked the whole population of Lima, and was fatal, particularly to old people, in consequence of grave pneumonias which were developed in its course. The first cases were observed from the middle to the twenty-four of July, and extended rapidly and simultaneously to all the inhabitants of this city, so that, during the height of the epidemic, the streets were deserted for ten or fifteen days.

REPORTED IN THE GACETA MEDICA DE LIMA,
JULY 15, 1858.

THE DIAGNOSIS OF ASTHMA IN INFANCY

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IT IS not unusual to see a baby who wheezes repeatedly with respiratory infections. Some of these have no other signs of allergy, and, after study, no signs of any other condition which might cause the wheezing are found. The questions then come up: Is this asthma? Should we treat him as if it is? The discussion of this problem is the purpose of this paper.

I should like to review some of the characteristics of asthma in infancy as seen in a study of my private patients. Seventy-nine patients with recurrent wheezing, seen before the age of 2 years, have been followed for more than two years. The records of these cases are not a fair sampling of those usually seen by a physician. During the first part of this period only the more severe cases were listed as asthma and the records of the milder ones were lost. During the last ten years I have also recorded the milder cases, but at this time the patients referred were doubtless more seriously affected than the average baby with asthma. Only scratch tests were made on most of these patients, and the intracutaneous tests that were done are not used in this report.

Two deaths occurred among patients seen during this period. One patient was seen only three times, and four years later I had the report of her death; the cause of death was not clear. A 10-month-old baby who had wheezing with respiratory infections, but no other signs of allergy, also died, apparently from an acute febrile disease. I did not see him in his terminal illness, but the autopsy was reported as showing bronchitis with some increase in eosinophils in the exudate around the bronchioles.

Cystic fibrosis of the pancreas was found in one patient. This patient one year later developed a strongly positive test to ragweed, and was worse during the ragweed season. This patient evidently has both fibrosis of the pancreas and asthma.

It was possible to demonstrate the allergic state in one group of 52 babies. Twenty-seven of these at some period showed atopic dermatitis, 34 had strongly positive scratch tests, 7 had obvious clinical response to exposure to some allergen, and 2 patients had many eosinophils in the nasal smear. These babies clearly suffered from asthma.

The second group was composed of 17 patients. These had no definite signs of the allergic state, but had suggestive signs, or what might be called circumstantial evidence. Thirteen of these had respiratory allergy in their immediate family, parents or siblings. Four others showed at least a 6 per cent eosinophilia in the blood.

Ten patients formed the third group, and in these, except for recurrent wheezing, there were no signs of allergy. Asthma seems the logical diagnosis, partly because the character and occurrence of the wheezing give the impression of the disease, and partly because treatment on the basis of allergy was effective. These babies with mild wheezing attacks and no other signs of allergy seemed to have the disease in a mild form and under treatment did very well.

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It is interesting to compare the results in the three groups. Of the first group, the 52 with demonstrable allergies, 31 (60 per cent) have had some wheezing during the last year of observation. This is not quite as bad as it sounds, as I believe that all are living comparatively normal lives, carrying on at school or work However, only 40 per cent of these patients are completely well. Of the second group of 17, with only circumstantial evidence of the allergic state, 12 (or 70 per cent) were entirely well for the last year. Of the third group of 10 with no signs of the allergic state, 8 (80 per cent) were entirely well. Statistics on such small numbers are hardly worth recording, but these figures at least do not contradict the idea that wheezing babies with no other signs of allergy have a milder form of asthma.

It is also evident that the more marked the evidences of allergy, the worse the prognosis. Eighteen patients who had eczema gave definite positive scratch tests. Of these, 13 (72 per cent) are still sick, at least to the extent of doing some wheezing during the last year of observation. Nineteen babies had a scratch test strongly positive to egg and, of these 19, all but 2 had some wheezing during the last year.

The records of the 6 most difficult cases in this series were studied. These patients now average 21 years of age, the youngest is 11 and the oldest 33. I found that these difficult-to-treat patients all had eczema and they all had positive tests including a strong reaction to egg when first studied in infancy.

The number of positive skin tests tends to increase with advancing age. Of the patients with negative or doubtful scratch tests, about half of those who were retested a year later showed definite positives. These latter tests were usually positive to inhalants.

A much more striking change was shown in the patients who originally showed positive tests to foods. With these almost invariably the food-positive tests diminished with successive tests and the inhalant-positive tests appeared and increased. These patients who react to foods appear to be better reactors, which probably represents a greater susceptibility to sensitization. In general, the patients with many positive tests, and with strongly positive tests, have more severe symptoms.

It has been stated that, in general, asthma in the beginning shows itself in attacks, with complete clearing in the intervals. This is not true in infancy. Almost half of my patients began with what was apparently a respiratory infection, and then wheezed continuously for a period from one to several months. This is true in both the group with proved allergies and the group without any proved allergies.

The important problem to be decided is the nature of the illness in babies with recurrent wheezing in whom no other pathologic condition can be found and in whom there are no demonstrable allergies. In favor of the diagnosis of asthma are the following points:

1. The general symptomatology in babies with demonstrable allergies and in those without known allergies is the same, except that in the latter the cases tend to be milder.
2. The babies with at first no signs of allergy other than the wheezing not infrequently develop other signs while under observation. It is not unusual to have a baby improve when in the hospital and become worse on return to his home, presumably because of environmental allergies.
3. Allergy treatment, including control of environment and the injection of vaccines, in most of these doubtful cases is strikingly successful.

SUMMARY

Some of the characteristics of asthma in infancy are reviewed. The attacks of asthma commonly occur with respiratory infections, and in many babies occur only with such infections.

More than half of these babies with recurrent wheezing did not have definitely positive scratch tests.

The babies with positive scratch tests and those with eczema usually had a more severe form of asthma than the others and the prognosis was poorer. Also, the more marked the signs of allergy, as shown by the number and degree of the positive tests and as shown by the severity of the eczema, the more intractable the asthma was likely to be.

The babies who had recurrent attacks of wheezing without other signs of allergy probably suffered from asthma of a lesser degree of severity in which the allergies were not readily demonstrable.

On Prescribing

''Venturesome medication,'' observes Dr. Hooker, ''is captivating, especially to the young and enthusiastic practitioner; and the charm is enhanced by the occasional brilliant achievements with which it is attended. Many of these achievements, however, are only apparent, being erroneously attributed to the remedies, when they are really the result of nature's efforts, and have been effected, perhaps, in spite of the agencies to which the credit is given. While the bold practitioner has this brilliant but often false show of success, the better results of the practice of the cautious physician commonly make but little display; yet, when he does attempt to produce decisive effects by his remedies, so definite is his aim, that the result may be calculated upon almost with certainty.''

FROM A PRIZE ESSAY BY WORTHINGTON HOOKER, M.D.,
NEW HAVEN. PUBLISHED, BOSTON, 1857.

WIDENED ROENTGENOGRAPHIC MEDIASTINAL SHADOW (THYMUS ?) AND ALLERGY IN CHILDHOOD

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THE study of the general characteristics of the allergic infant and child is important, because, if it is suspected that allergic disease is likely to develop, appropriate prophylactic measures may be instituted.[6] Waldbott and Anthony[11] in 1934 reported that in 30 children in whom roentgenograms had shown what was diagnosed as an "enlarged thymus," a follow-up study revealed that 24 were afflicted with an allergic disease and in 4 more such a diagnosis was questionable. Later the same year, Tumpeer[9] also made the observation that roentgen evidence of a widened mediastinal shadow, presumably in most instances indicating an enlarged thymus gland, occurred with significant frequency in children in association with allergic disease. However, he presented no statistical analysis of his series. Waldbott and Anthony[11] and Waldbott[10] drew attention to similarities in the pathological findings between infants dying of anaphylactic shock and infants reported to have died because of an "enlarged thymus." This suggested that so-called "thymic death" is actually death from anaphylactic shock. Carr[3] in 1945, in cases of so-called "thymic death," noted the same type of anatomical and cytological abnormalities as those previously described by these authors. In view of the foregoing, it was felt that, if an unusually broad mediastinal shadow on the roentgenogram could be interpreted as suggestive evidence that one was dealing with an allergic child or a child likely to develop allergies, at least one small facet might be added to the weight of evidence as to whether or not any given infant or young child might eventually develop allergic disease. The opportunity for making such a study presented itself when Simpson and associates[7] began to investigate the late effects with respect to neoplastic disease in those infants who had received roentgen treatment in early infancy for what was thought to be a large thymus gland.

It is important to remember that the great majority of children reported upon by Simpson and associates were diagnosed as suffering from thymic hyperplasia a number of years ago when almost any sudden death in early infancy of which the cause was not immediately obvious was attributed to asphyxia caused by an enlarged thymus gland. Probably the most complete study of this subject is that of Crotti.[5] The signs and symptoms which led one to examine the thymus roentgenographically were

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principally unusual respiratory abnormalities such as variations in the rhythm of respiration, stridors, cyanosis, choking, or any other form of dyspnea. Physicians and the lay public alike were very much concerned with this problem, and, in some hospitals, all newborn infants were routinely subjected to roentgen study for a large thymus gland and some physicians demanded this before elective surgery in children.

The concept that enlargement of the thymus gland may be associated with sudden death has always been received with skepticism by many students of this subject, but the report of the Status Lymphaticus Investigation Committee[13] in 1931 delivered the first really powerful blow to this concept. This Committee concluded that there was no real evidence that the thymus gland was responsible for occasional sudden death. This opinion is generally accepted at the present time. It is not the purpose of this communication to discuss this subject further. Those interested are referred to the observations by Caffey,[2] and the comprehensive studies and reviews by Adelson and Kinney[1] and others.[4, 8, 12] The pendulum in medicine, however, often swings from one extreme to the other until incontrovertible facts are finally established. Until it is definitely shown that angioedema of the thymus gland resulting in death because of pressure on the trachea or the vascular structures at the base of the heart *never* occurs, we feel that an open mind should be kept with regard to this possibility, even though it may be one of the most rare occurrences in medicine.

Our material, which was gathered in the course of the study by Simpson and associates,[7] consists of 614 newborn or very young infants in whom the diagnosis of thymic hyperplasia had been made by the roentgenogram. These cases were taken serially from files made available by radiologists and pediatricians of the city of Rochester, New York. The members of this group were treated by x-ray from two to twenty-seven years prior to 1953. The controls consist of the untreated siblings, and the group as a whole may be considered representative of the heterogenous population of a northern metropolitan American city.

The information relating to the present health of these patients and their untreated sibling controls was obtained largely from a questionnaire sent to the parents. When possible, the information was supplemented by hospital records. It was realized that the questionnaire method of follow-up has many pitfalls, so only three simple questions were asked. These concerned whether or not the patient or a sibling had ever developed bronchial asthma, hay fever, or eczema. No additional questions relative to other possible allergic phenomena or other family history of allergy were posed, and the conclusions were based on the answers to the questionnaire.

The cases are summarized in Table I. Of the 614 children who had been

TABLE I

	NUMBER	PER CENT
Total patients treated for "thymic enlargement"	614	
Patients who subsequently developed allergic disease	173	28.2
Total siblings of patients with "thymic enlargement"	1,287	
Number of siblings who developed allergic disease	106	8.2

treated for what was diagnosed as an enlarged thymus gland, the follow-up study showed that 173, or 28.2 per cent, were later afflicted with one of the above-mentioned major allergic diseases. In the control group of 1,287 siblings, only 8.2 per cent developed such allergic diseases.

COMMENT

It seems fair to state, even though in most instances there were no roentgenograms in the sibling control series, that children who show broad mediastinal shadows roentgenographically, with or without symptoms, which were formerly attributed to an enlarged thymus gland, develop allergic disease significantly more frequently than children who either do not show such a shadow or have had no such symptoms. This brings up the intriguing possibility that symptoms formerly attributed to the presence of an enlarged thymus gland may in fact, in many instances, have been early symptoms of allergic disease. This might, since the symptoms are respiratory in nature, be confirmed by the finding of eosinophils in the postnasal smear or by the therapeutic trial of antiallergic measures such as the use of sympathomimetic drugs, antihistamines, elimination diets, environmental control, etc. The so-called enlargement of the thymus gland may, also, in the allergic or potentially allergic child, be merely a part of the general lymphoid hyperplasia, which characteristically occurs in many allergic children, particularly as regards the tonsils and adenoids.

CONCLUSIONS

The presence of an unusually broad mediastinal shadow presumably due to the presence of an enlarged thymus gland or the presence of respiratory symptoms which could conceivably be attributed to the presence of an enlarged thymus gland is reasonable presumptive evidence that such a child is more likely to develop subsequent allergic disease than a child who does not present such findings.

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GROUP SESSIONS FOR PARENTS OF CHILDREN WITH EPILEPSY

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THE need for a consistent and organized educational program for parents of children with epilepsy has been recognized for some time. The children and parents seen by the psychologist in the Psychiatric Clinic as a part of the integrated service of the Clinic focused attention upon this need. The Jerry Price Seizure Clinic of the Los Angeles Childrens Hospital instituted a program of orientation for parents of children with epilepsy by means of group sessions in March, 1955. This program is believed to be original and the first to be described in this country. Its success and the parent response have been encouraging. We are reporting the outline of the sessions in the hope that such a program, or similar group sessions, might be useful in other clinics.

The primary aim of the group sessions is the correction of prejudice and misunderstanding, and the relief of tension in the parents of children with epilepsy, which is an important part of the over-all therapy. Prior to the institution of group sessions, this function was handled by the physician during the clinic visits. Epilepsy and the principles of its treatment were explained.

The social worker worked with some of the parents at the request of the physician and the psychologist. The psychologist's role was limited to seeing those parents referred to the Psychiatric Clinic by the physician for emotional or intellectual evaluation. In some instances, this was followed by therapy sessions with the psychologist.

The frequency and consistency of questions and problems presented by the parents relative to the care of such children became apparent to the members of the clinic. The presence or absence of serious emotional or intellectual disturbances in the child did not influence the parent's primary concerns. Parents were noted to have concepts of a child's illness clouded by misunderstanding after as much as two years' attendance in the clinic. It was concluded that this phase of the medical care was obviously weak.

The success of group therapy in other fields encouraged us to feel that the technique might be applied to this problem. The concept of group sessions was suggested by the psychologist who is a regular member of the Seizure Clinic staff.

In order that epilepsy might remain the primary subject, it was elected to exclude those parents whose children had, in addition, cerebral palsy, blindness, severe hearing deficiency, diabetes, marked mental retardation, or other gross disorders. It was felt that the group discussions would become too complex if such additional conditions were brought up by the parents.

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There is particular reason to avoid the suggested association of mental retardation and epilepsy to the parent of a child with average intelligence.

OUTLINE OF GROUP SESSIONS

After some experimentation, the following procedure was adopted. Excluding the parents of children with the above-mentioned additional problems, the parents of all new patients to the Seizure Clinic are interviewed by the social worker after the first visit with the doctor. At this time the orientation course is outlined and the importance of regular attendance for the sake of continuity is emphasized. Transportation, "sitter," and working time problems may be involved. If these things can be arranged, an appointment is made for the next available series of sessions.

The course consists of five weekly meetings, lasting from one to one and one-half hours. Registration is limited so that the parents of no more than eight children participate. The atmosphere is that of round-table discussion with questions and interruptions welcomed. At the first two sessions, one of the clinic physicians, a pediatrician as well as an epileptologist, speaks on the medical aspects of epilepsy. At the next two sessions, the psychologist discusses the management of the child, the emphasis being on the child rather than on epilepsy. The focus of the last session is the relationship of the child within the total family group and the community, with the social worker leading the discussion. The psychologist and the social worker are present at all the sessions and have the opportunity to observe those parents who may benefit from additional help on an individual basis.

To encourage the thorough participation of the parents, all distracting factors are eliminated. Observers are excluded, as are the children. It is desirable to keep the situation from reverting to that of the clinic visit or lecture room.

First and Second Sessions.—At the first two meetings of the group sessions, conducted by one of the clinic physicians, the primary purpose is to introduce the parent to the clinic and to give him reliable information concerning epilepsy and its treatment. A brief description of epilepsy and its treatment is outlined. The diagnostic devices and techniques used in arriving at this diagnosis are explained to the parents and their questions are answered. The different kinds of seizures, their frequency and duration are described. The principles of medication and treatment are discussed. That these medications are not habit forming is emphasized especially. The parents are instructed in the care of the child during convulsions.

Parents are encouraged to ask questions whenever they desire. Recurring questions relative to specific aspects of epilepsy will indicate the need for further discussion of particular problems. Typical questions which indicate the primary concerns of parents are as follows: To what extent should physical activity of the child be curtailed? Will the child die in a convulsion? Will he recover? Is epilepsy hereditary? Will the convulsions cause heart damage? Will they lead to nervous or mental illness? What adverse effects, if any, may be expected from the medication?

In the informal discussions it is felt the parent obtains a clearer conception of the problem. Through accurate specific knowledge he rids himself, to some extent, of prejudices and misconceptions associated with epilepsy, and gets practical help in learning to care for the child. That he is able to share his problems with others in some measure gives the parent support at an important time, that is, when treatment of the child is being instituted and the parent is adjusting to the care of the child with this condition. The group sessions with the physician are essentially factual and informative.

Third and Fourth Sessions.—The psychologist introduces a new phase in parent education and therapy in the third and fourth group sessions. Practical and specific advice on management problems are considered. These two sessions also serve as a screening device for disturbed family situations that could be handled more effectively early in the patient contact with the clinic. The parent is given the opportunity to ventilate his feelings in the group sessions, and he is then encouraged to examine them. Criticism or support from other parents has a salutary effect upon the parent. The psychologist structures these sessions according to the needs of the group.

Two major concerns are consistently apparent in the sessions with the psychologist. Discipline is the primary problem of these parents. Parental insecurity and uncertainty are frequently apparent relative to control of the child's behavior, especially when administration of discipline appears to precipitate a seizure. Discipline is discussed in its general aspects. The parent is encouraged to ask questions about his particular situation. He can thus present his feelings and attitudes to the psychologist who, with the aid of the group, works at making him feel more comfortable with the idea of discipline. He is made more aware of feelings he may have which interfere with discipline. Attitudes are subject to critical inspection and all members of the group are invited to participate in this procedure.

The second most important problem is behavior, normal and abnormal.

Parents of children with epilepsy are sensitive to what they think might be a deviation from the normal. An attempt is made to point out reasons for a child's behavior other than the fact that he has seizures. The object is to allow the parent to accept the idea of individual behavior as a rational part of the growth process in every child, including his own.

Another subject that generally needs discussion is the parent's attitudes and emotional conflicts about epilepsy. The objective atmosphere of discussion and criticism aids the parent in attaining perspective necessary to free himself of unhealthy attitudes. Relieved of these he will be able to offer the child increased emotional support.

Other topics discussed are the fear of convulsions, overprotectiveness, and relations of the child with other children in the family. The child's emotional development is largely a result of the emotional relationships he has within the family, and this is stressed to the parents. The goal of the group sessions with the psychologist is to help the parent accept the problem of his child's having epilepsy more intelligently and objectively. The parent will then be able to give him the necessary emotional support and special care that this particular problem presents.

Fifth Session.—The social worker conducts the fifth and final session of the group sessions which is concerned with total family life and social adjustments. At this meeting the parents are given suggestions about interpreting the term "epilepsy" to relatives, neighbors, and friends. Information is given about available resources of the community, public school programs, camp facilities, and community groups interested primarily in epilepsy. At the conclusion of this session, parents are given a brochure to take home.

The brochure is written in nontechnical language and is a summary of much of the medical and psychological information covered during the group sessions. It was compiled on the basis of typical parent questions and concerns that had been observed and recorded during the first year of group sessions. The parent is encouraged to read it and to bring back to the clinic further questions he may have. The continuing interest and help of the Social Service Department is emphasized to the parents for any future problems they may have.

SUMMARY

1. At the Jerry Price Seizure Clinic of the Los Angeles Childrens Hospital, the need for a consistent and organized educational program for parents of children with epilepsy was recognized. Customary clinic visits with the doctor were inadequate for this purpose. Courses of group sessions were initiated. This procedure has been carried out for two years and has been found effective in its original aims.

2. It is felt that the parents of children with epilepsy are able through the group sessions to correct their misunderstandings and prejudices and relieve their tensions to some extent.

3. The course is divided into five sessions and attendance is limited to the parents of eight children. The first two sessions are conducted by a physician who is also an epileptologist. At these sessions the physician deals with essentially factual and informative material. He encourages the parents to ask questions and answers them informally. Group discussions are emphasized.

4. The next two sessions are conducted by the psychologist. The two most frequently discussed problems are discipline and behavior. Through discussion and ventilation the parents are helped to accept the problem of the child with epilepsy more intelligently and objectively, resulting in increased emotional support for the child.

5. The final session is conducted by the social worker, who focuses attention upon the child's social relationship and informs the parent of the facilities and services available to them for help with the child. The continuing interest of the Social Service Department in any future problems that may arise is likewise emphasized.

6. It is believed, after a period of more than two years, that the group sessions for parents of children with epilepsy are of material aid and have fulfilled the objectives for which they were designed.

THE TRACE ELEMENT SELENIUM AND ITS INFLUENCE ON DENTAL CARIES SUSCEPTIBILITY

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RESEARCH concerning the influence of trace elements on the susceptibility to dental caries has been mainly confined to the study of fluorine. For the past several years, a great number of studies have appeared in the literature on the different aspects of the fluorine-dental caries relationship. As a result of this, fluoridation of communal water supplies has been accepted as an effective and safe public health measure for the partial protection against dental caries.[1] However, the possibility that other trace elements may play a role, beneficial or harmful, on the degree of susceptibility to dental caries observed among different population groups has not received adequate attention by research workers. That this area presents a promising field for investigation has been indicated from studies conducted with experimental animals.[2-4]

The employment of the epidemiological principles and techniques for the study of dental caries has been recognized as an effective research tool.[5, 6] During the last few years, a number of regional epidemiological studies on dental caries were conducted in Oregon among native-born and -reared children. These investigations were undertaken in 10 counties located east and west of the Cascade Mountain Range, which divides the state of Oregon into two distinct areas from the point of climatology, agriculture, and topography. Furthermore, it is known that the fluoride content of most of the public water supplies of Oregon is negligible.[7] Dental examinations were given to 2,069 children between the ages of 14 and 16 years who were born and had lived continuously in their respective counties. All examinations were performed by one examiner (D. M. H.), a fact which adds uniformity to the collected data. A complete picture of the results of these studies has been presented in the latest article of this series published recently.[8]

One of the outstanding findings of our epidemiological investigations was the existence of a direct relationship between urinary selenium concentration and dental caries prevalence.[9] The results obtained indicated that the trace element selenium may render the teeth more susceptible to dental caries attack. Thus, for the first time, evidence was presented suggesting that a trace element, selenium, may be responsible for increasing caries susceptibility. In view of the above, it was deemed advisable to undertake

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further research for the purpose of eliciting additional knowledge on the selenium-dental caries relationship. This paper gives the results of a second study conducted among Oregon school children on the association between urinary selenium concentration and caries prevalence.

METHODS AND RESULTS

The present investigation on the selenium-dental caries relationship was undertaken among school children living in the counties of Jackson and Josephine of the Southern Oregon Region. The results of a recent epidemiological study, published elsewhere,[10] revealed that children 14 to 16 years of age born and reared in the above-mentioned two counties showed a high degree of susceptibility to dental caries. Moreover, the caries experience among the subjects of both counties was found to be similar, that is, 13.4 D.M.F.* teeth per child in Jackson county and 14.4 D.M.F. teeth per child in Josephine county.*

For the purposes of our study, 24-hour urine specimens were collected from white male high school children who were continuous residents in each of the two counties. Experimental work with laboratory animals has shown that a definite relationship exists between the amount of selenium ingested and the excretion level of this trace element in the urine.[11]

Altogether, 79 urine specimens were collected from both counties. Of these, 33 belonged to children attending the high school of Medford, county seat of Jackson county. The remaining 46 were collected from boys attending the high school of Cave Junction. This school serves families from a rural area in Josephine county. The selection of children for inclusion in the study was done by the principals of the participating high schools, and it was based on their personal knowledge regarding each subject's cooperation and reliability.

Each boy participating in the study was given a one-half gallon Mason jar, and was asked to take it home for collection of a 24-hour urine specimen during the week end. In addition, the subjects were given verbal and written instructions for the proper collection of the urine specimens.

In the determination of urinary selenium the procedures of our first study were followed for digestion, distillation, and precipitation of selenium.[9] Subsequently, the method of Coleman and McCrosky was followed with minor modifications.[12] The selenium was filtered, washed, and the small filtering tubes were transferred to side-arm test tubes. The selenium was then dissolved in 3 ml. of 0.05 per cent bromine in 30 per cent hydrobromic acid and washed into the test tube with 5 ml. water. Excess bromine was reacted with phenol and the selenious acid titrated with 0.001 N thiosulfate and iodine.

The distribution of urinary selenium concentrations among the children included in the present study is given in Table I. The results of the analyses revealed that selenium was present in all the urine specimens collected from the subjects of both counties. The mean urinary selenium concentration of children living in Jackson county was found to be 0.074 p.p.m. and that of subjects in Josephine county 0.076 p.p.m. These values are regarded as being of considerable magnitude and show a definite selenium intake.

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*The symbol D.M.F. denotes the number of teeth which are Decayed, Missing, Filled.

TABLE I. DISTRIBUTION OF URINARY SELENIUM CONCENTRATION AMONG CHILDREN LIVING IN JACKSON AND JOSEPHINE COUNTIES OF OREGON

JACKSON COUNTY		JOSEPHINE COUNTY	
SE (P.P.M.)	NUMBER OF SUBJECTS	SE (P.P.M.)	NUMBER OF SUBJECTS
0 – 0.019	3	0 – 0.019	2
0.020 – 0.039	6	0.020 – 0.039	3
0.040 – 0.059	4	0.040 – 0.059	10
0.060 – 0.079	6	0.060 – 0.079	13
0.080 – 0.099	6	0.080 – 0.099	8
0.100 – 0.119	5	0.100 – 0.119	6
0.120 – 0.139	1	0.120 – 0.139	3
0.140 – 0.159	1	0.140 – 0.159	0
0.160 – 0.179	0	0.160 – 0.179	1
0.180 – 0.199	1	0.180 – 0.199	0
Mean 0.074 ± 0.007*		Mean 0.076 ± 0.005*	

*Standard error of the mean.

It is of interest to note that the mean values of urinary selenium excretion among the children of both counties are similar. As it was indicated above, the dental caries experience (mean D.M.F. teeth) of children in the counties of Jackson and Josephine was also found to be similar. In addition, the percentage of subjects in Jackson and Josephine counties with values of urinary selenium excretion above 0.100 p.p.m. is about the same, 24 per cent and 22 per cent, respectively. It thus appears that high prevalence of dental caries is associated with high values of urinary selenium excretion.

DISCUSSION

The results of the present investigation, together with those of our first study, among Oregon school children on the selenium-dental caries relationship provide data which suggest the possibility that this trace element may be responsible for increasing caries susceptibility.

Interest in the trace element selenium by research workers is of relatively recent origin. Selenium became the subject of extensive investigation since it was discovered in the early thirties to be responsible for livestock poisoning in a number of western states. The possible ill effects of selenium intoxication on population groups have been largely unexplored. However, the hazards to health from the continuous daily ingestion of small amounts of selenium have been recognized. Selenium is considered to be a normal constituent of the soil and is absorbed by all vegetation at least in minute amounts. A number of investigations regarding the selenium sources in seleniferous areas revealed the presence of this element in vegetables, cereal grains, foods of animal origin, and water.[13] Since selenium is widely distributed in nature, it is normally present in enamel in small amounts.[14]

In recent years, Lemley[15] and Lemley and Merryman[16] reported on a number of cases of selenium poisoning in human beings that apparently resulted from the daily ingestion of foods grown in seleniferous areas. In one of their patients the presence in his urine of about 0.040 p.p.m. of selenium was considered to be evidence of selenium poisoning. In view of the above, it is of interest to note that in the present study values of urinary selenium excretion of 0.040 p.p.m. and higher were found in the majority of the subjects (Table I). However, it should be mentioned that at the present time no adequate information is available regarding levels of urinary selenium excretion indicative of selenium poisoning.

The possible relationship between selenium and dental caries susceptibility has not been investigated adequately. Smith and his co-workers conducted two field surveys among people residing in certain seleniferous regions in an attempt to discover symptoms of disease associated with selenium poisoning.[17, 18] They found that "bad teeth, varying from marked discoloration through all stages of decay" was one of the most frequent signs of ill health among the people examined. Dogs treated with two goitrogenic compounds, selenium and thiouracil, showed structural changes in their dentition and jaws.[19] Wheatcroft and collaborators[20] investigated the effects of selenium on the dentition of white rats. Selenium was given intraperitoneally to three groups of rats at daily doses of 1 mg., 0.5 mg., and 0.2 mg. per kilogram of body weight together with a cariogenic diet. At the end of the experimental period they observed a trend toward an increase of caries incidence among the animals receiving the most selenium.

It thus appears that in a manner as yet unknown the trace element selenium may be a factor contributing toward an increased susceptibility to dental caries. Undoubtedly, a number of additional studies with experimental animals and human beings are necessary, not only for confirmation of the relationship suggested here but also for an understanding of the exact mechanism through which selenium may exert its harmful effects on teeth.

SUMMARY

An investigation of the possible relationship between the trace element selenium and the degree of susceptibility to dental caries was conducted among Oregon school children.

The findings of the present investigation, as well as those obtained from our first study, indicate that selenium may be a factor responsible for increasing the susceptibility to dental caries attack.

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The Composition of Breast Milk

An infant three months old will take from forty-eight to sixty-four fluidounces daily in six or eight half-pint doses. During the first year therefore he will take from 1000 to 1300 lbs.

What is the composition of this milk? Without entering this long and tedious details, it may be simply said that by the latest and apparently the most exact analysis, its composition is:—

Butter	20.76	1000 lbs. therefore contain	Butter	20.76 lbs.	1300 lbs. therefore contain	Butter	27 lbs.
Casein	14.34		Casein	14.34 "		Casein	18½
Sugar	75.02		Sugar	75.02 "		Sugar	97½
Water	889.88		Water	889.88 "		Water	1157

In 1000 lbs. of milk there are 1.6238 lbs. of salts, or 26 ounces, of which 0.5736 lb., or 9 ounces, are phosphate of lime.

In 1,300 lbs. of milk the salts amount to 2.1 lbs., or 33½ ounces, of which 12 ounces are phosphate of lime.

It thus appears that, during the first year, the child receives from 110 to 143 pounds of dry solids. He may thus readily gain 15 or 20 pounds in weight (implying less than three pounds of dry solids), and yet have a large residue, from 107 to 140 pounds, to be expended in the production of heat and in the activity of an energetic vitality. A child thus nourished can make teeth and bone without difficulty; his functional activity need never be suspended for want of material; atmospheric changes may be successfully resisted, and zymotic diseases will have little power.

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TESTOSTERONE-INDUCED FEMALE PSEUDOHERMAPHRODISM

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SINCE Wilkins and his group[1] established clinical and laboratory evidence that cortisone suppresses the signs and symptoms of congenital adrenal hyperplasia, a great deal of study has resulted in increased understanding of hermaphrodism.

Female pseudohermaphrodism is characterized by an enlarged penislike clitoris, partial or complete fusion of the labia majora in the midline, and a urogenital sinus. Differentiation between congenital adrenal hyperplasia and the nonadrenal forms of pseudohermaphrodism cannot be made on examination of the external genitals. The distinction is made by the demonstration of excessive androgen production in congenital adrenal hyperplasia as evidenced by elevation of the level of 17-ketosteroids and pregnanetriol in the urine.

Patients with nonadrenal female pseudohermaphrodism have normal plasma and urinary 17-ketosteroids and the absence of no abnormal quantities of pregnanetriol in the urine, and at puberty have normal female sexual maturation with menstruation. A total of 14 cases have been described in the literature. In 2 cases[2, 3] the infants were born to mothers with arrhenoblastomas, and it appears that the virilization was a consequence of excessive androgen secretion by the neoplasm. Recently Grunwaldt and Bates[4] and Hayles and Nolan[5] have reported 2 cases of testosterone-induced female pseudohermaphrodism which is similar in many respects to the case to be described. The etiology of the masculinization in the other cases is not known.

This report deals with a case of female pseudohermaphrodism which we believe was induced by the administration of testosterone to the mother during the first trimester of pregnancy. It is the purpose of this paper to emphasize the danger of testosterone administration during the childbearing period.

CASE REPORT

History.—K. C. (CH No. 113941), born July 3, 1957, was admitted to the Children's Hospital on Aug. 8, 1957, at 36 days of age. The mother's prenatal course was characterized by low back pain and an orthopedic surgeon was consulted during the first weeks of pregnancy. X-ray examination showed some decrease in mineralization of the vertebrae. After approximately six weeks of pregnancy, the mother was given orally 30 mg. of methyltestosterone and 3.75 mg. of Premarin daily. This medication was administered for a total of six weeks between the seventh and fourteenth weeks of gestation. The mother, therefore, received a total of 1.26 Gm. of methyltestosterone during the first trimester of pregnancy. The remainder of the pregnancy was uneventful except for the fact that during the fourth month the mother fainted, pulling a washtub on her abdomen.

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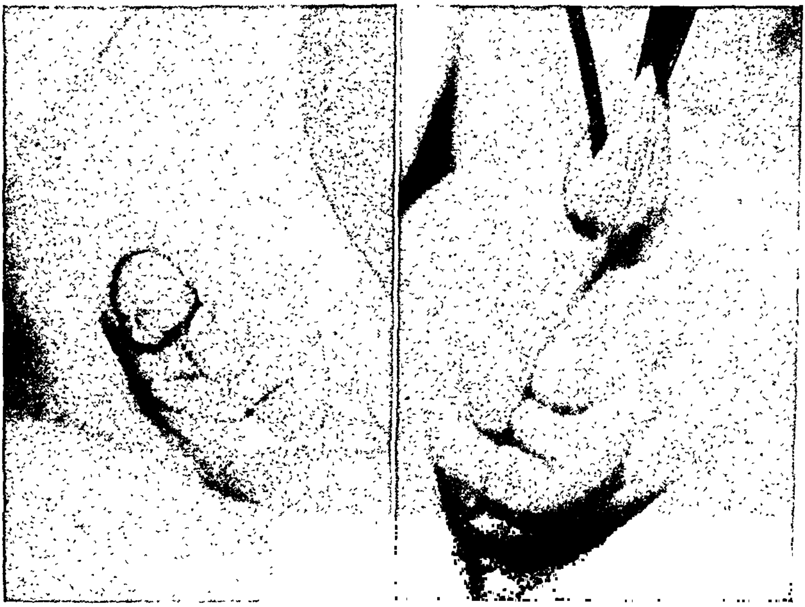
Because of the temporary absence of fetal heart tones, she was hospitalized for a two-day period.

The delivery was normal and the patient weighed 8 pounds at birth. Except for the absence of testes, the genitals had a normal male appearance. The infant was noted to have a large abdominal mass and after unsuccessful catheterization a cystotomy was performed at 2 hours of age; at this time, a double cystic cavity was entered and a biopsy taken. The anterior cavity contained urine; when this was decompressed, the posterior cavity bulged forward. This contained a mucinous fluid. Biopsy from the posterior cystic cavity revealed squamous epithelium consistent with vaginal mucosa. On the fourth day of life a cystogram was performed; during the procedure a membrane ballooned through the urethral meatus which presented at the tip of the phallus. This membrane ruptured spontaneously and urinary drainage was established per urethra. The infant was discharged from the hospital at 10 days of age, but was readmitted at 26 days of age with the clinical pictures of a urinary tract infection. "She" was then transferred to the Children's Hospital.



A. *B.*

Fig. 1.—*A*, Appearance of external genitals. *B*, Appearance of external genitals. Note catheter in penile urethra.

Physical Examination.—With the exception of the external genitals and a well-healed suprapubic scar, physical examination was essentially normal. Examination of the genitals (Fig. 1,*A* and *B*) showed a phallus measuring approximately 2 cm. in length, with a small central meatus. The corpora of the phallus were felt at the base. The labia were fused in the midline and had a scrotumlike appearance. No gonads could be palpated within the scotum or in the inguinal canal.

Laboratory Findings.—The hemogram was essentially normal. Repeated urinalysis showed albumin in amounts up to 4 plus and many white

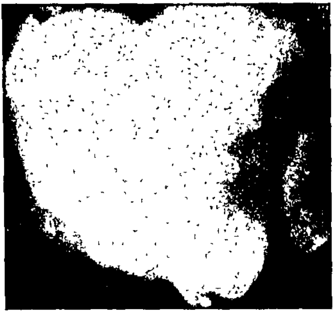
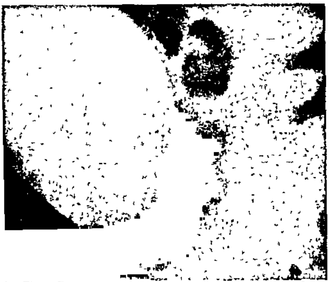


Fig. 2.—Initial "cystogram," anteroposterior projection. Appearance of double bladder simulated by distended bladder and vagina.

Fig. 3.



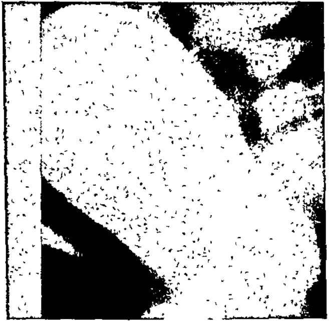


Fig. 4.

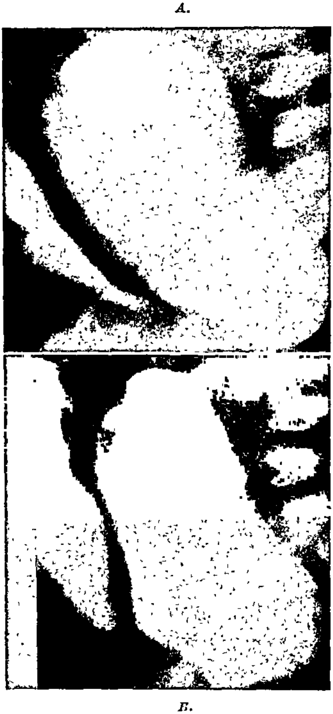


Fig. 5.—*A* and *B*, Spot films showing reciprocally varying stages of distention of bladder (anterior), and vagina (posterior) during spontaneous emptying from one into the other.

blood cells. Urine cultures grew *Aerobacter aerogenes, Pseudomonas aeruginosa,* and *Proteus mirabilis.*

Fig. 3.—Spot film during filling of bladder under fluoroscopic control (lateral projection). The catheter has entered a normally located bladder, which is distended by contrast substance. Note the clear space between the posterior border of the bladder density and the vertebral column.

Fig. 4.—Spot film during [illegible] fter filling [illegible] 3. The [illegible] the smal [illegible] rior to th [illegible] latter fi [illegible] Fig. 3. N [illegible] to the [illegible] ows slow, [illegible] der.

Routine chemistry determinations were within normal limits.

Twenty-four-hour urinary 17-ketosteroids on two occasions were 1.1 and 1.5 mg. and the 17-hydroxycorticoids were 6.3 mg. Repeat studies in another laboratory showed 0.18 mg. 17-ketosteroids and less than 0.1 mg. pregnanetriol per 24 hours.* White blood cells and buccal smears indicated that the patient was of the female genetic sex. An excretory urogram was interpreted as indicating a mild obstructive uropathy with hydroureter and hydronephrosis on the left. A cystogram (Figs. 2, 3, 4, and 5*A* and *B*) showed the presence of two large communicating chambers; these were interpreted as an anterior urinary bladder and a posterior vagina opening into a urogenital sinus. A survey of multiple ossification centers[6] showed normal bone age.

Hospital Course.—The patient was given multiple antibiotics for the urinary tract infection and had a complete clinical and laboratory cure.

Exploratory laparotomy (Fig. 6.) disclosed a dilated bladder and vagina communicating with a urogenital sinus. At the apex of the vagina there were an infantile uterus, tubes, and cystic ovaries. Biopsy specimens taken from each ovary showed immature ovaries with follicle cysts. A partial cystectomy and plastic reconstruction of the urethra were performed.

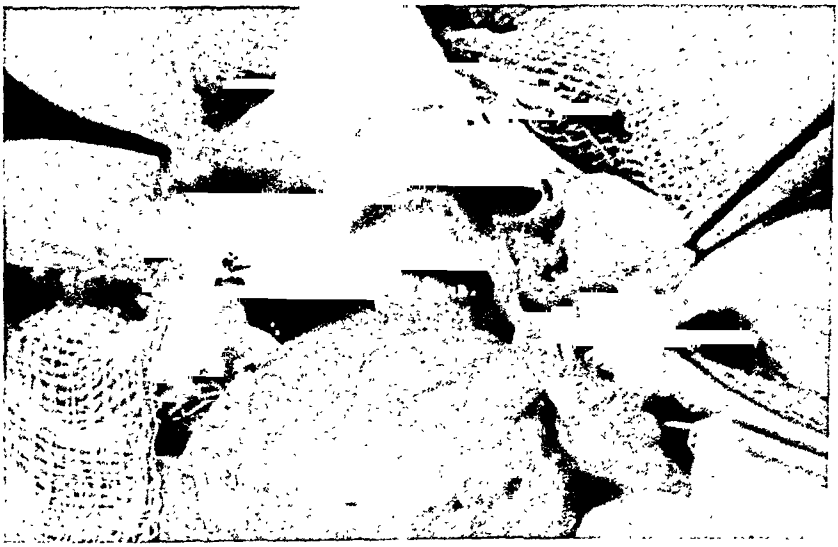


Fig. 6.—Appearance of normal female internal genitals at laparotomy.

Following these studies, the sex of rearing was changed to female and a clitorectomy and plastic reconstruction of the vagina are planned for some future date.

DISCUSSION

Testosterone administered to the mother during the first trimester of pregnancy appears to be the underlying cause of female pseudohermaphrodism in this patient.

Until recently there had been no adequate explanation for the pathogenesis of nonadrenal pseudohermaphrodism. Wilkins[7] theorized that some masculinizing agent must be present during the critical period when the external genitals were differentiating. He felt that one possible explanation was the temporary overactivity of the fetal adrenal which was subsequently normal at birth. The critical period is during the second and third months of fetal development, for by the fourteenth week the penile urethra has closed as far as the glans.[8] This hypothesis was rejected by Perloff and associates[9] because it failed to explain the renal anomalies in their patient. In the patient described in this paper, the associated renal anomalies can be explained on the basis of mechanical obstruction by the enlarged bladder and vagina.

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*Confirmatory determinations were performed by Dr. Alfred Bongiovanni, Children's Hospital of Philadelphia. During the immediate neonatal period the normal urinary output of 17-ketosteroids is 1.2 to 2.5 mg. per day, and this decreases to 0.5 mg. per day by the end of the first month of life. The normal 24 hour urinary excretion of 17-hydroxycorticoids is 3.3 to 9.3 mg. and pregnanetriol is found in trace amounts.

As further evidence that androgenic products can produce female pseudohermaphrodism, Greene and co-workers[10] have shown that administration of androgenic hormones to pregnant animals will produce genital anomalies in the offspring closely resembling those seen in this patient. Experimentally the production of these anomalies was dependent upon the period of gestation and the amount of androgenic substance given. It has been shown that the androgenic manifestations are limited to the external genitals without apparent effect on the ovaries, tubes, and uterus.

Since testosterone and related products are used extensively in clinical medicine, the possible danger arising from its use during the childbearing age should be carefully weighed.

We wish to thank Dr. A. A. Weech and Dr. F. N. Silverman for their helpful suggestions and encouragement.

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COBALT-INDUCED GOITER WITH CARDIOMEGALY AND CONGESTIVE FAILURE

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SINCE the discovery of cobalt as an integral part of the vitamin B_{12} molecule, its ability to produce remission in various types of anemia has been reported. Particular interest in pediatrics has centered around the treatment of iron deficiency anemia and the anemia of prematurity. Initial reports[1] were favorable, but the danger of toxic effects has been stressed more and more.[2] These toxic effects were first brought to our attention by the story of a child who was referred to a private pediatrician because of difficulty in respiration. The goiter was so large and firm that surgical exploration was done. At biopsy an erroneous impression of a carcinoma was made, and a complete thyroidectomy was performed. The child now requires thyroid replacement therapy and is getting along well. In retrospect the pediatrician accidentally learned that her parents were giving her, on their own, an "iron and cobalt tonic."†

Shortly after this, two other patients with similar complaints were reported by private pediatricians in Louisville. These goiters responded very quickly to the discontinuance of the cobalt and iron preparation which they had been receiving. The fourth case of a similar character has been seen in this clinic.

The fifth case which has come to our attention is the case being reported. The rather widespread use of this preparation among physicians with whom this case has been discussed, despite the reported danger of the indiscriminate use of cobalt-iron preparations, prompted this report.

CASE REPORT

D. P. B., aged 6 months, was referred to the Children's Hospital because of a bulging fontanel. He apparently had been well except for slow weight gain until about one week prior to admission when he had developed low-grade fever, dry cough, and hoarseness. Shortly afterward, tetracycline was prescribed, and after about five days the bulging fontanel was noted.

Past history revealed that the child was the result of a normal term pregnancy, but had gained weight slowly and had been noted to have some rapid respirations. He had been tried on a multitude of formulas including milk substitute formulas, without apparent success. He had always been a slow eater but had never had any vomiting and had had only one bout of mild diarrhea. The family history was noncontributory.

The patient had been diagnosed as having an iron deficiency anemia and

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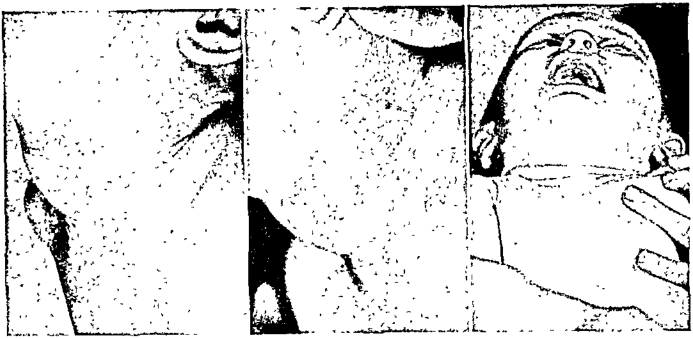
†Roncovite.

had been receiving "iron" therapy for three months.

Physical examination revealed a pale child who was breathing rapidly and appeared chronically ill. He weighed 10 pounds 8½ ounces and was 61 cm. long. His cardiac rate was 120 and his respiratory rate 50 per minute. Blood pressure studies revealed a systolic pressure of 80 mm. Hg by the flush technique, and this pressure did not change appreciably during the hospital stay. The anterior fontanel was noted to be full but not bulging. The skin was somewhat pale and he was cyanotic about his mouth. The external jugular veins were prominent even when the patient was placed in a forty-five degree position, and a remarkable firm mass was noted to fan out from the midline in the area of the thyroid (Fig. 1, *A*). This mass was firm and movable. No bruit or thrill was noted. The remainder of the ear, nose, and throat examination was negative. The respiratory rate was regular but rapid. The lung fields were clear to percussion. Fine crepitant râles were heard throughout both lung fields. There were no shocks or thrills. The point of maximal impulse was in the fifth intercostal space at the anterior axillary line. On auscultation the rhythm was regular. The heart sounds were faint and distant but no murmur was present. The liver edge was felt 6 cm. below the right costal margin in the right midclavicular line. The spleen was palpable about 3 cm. below the left costal margin in the flank. There were no other masses. The genitalia were considered normal. Reflexes were normal and radial and femoral pulses were easily palpated.



A. *B.* *C.*

Fig. 1.—The tumor (*A*) on admission; (*B*) three weeks later, and (*C*) seven months later.

The local physician was contacted and the iron preparation that had been prescribed was Roncovite, one-half dropper full twice a day.

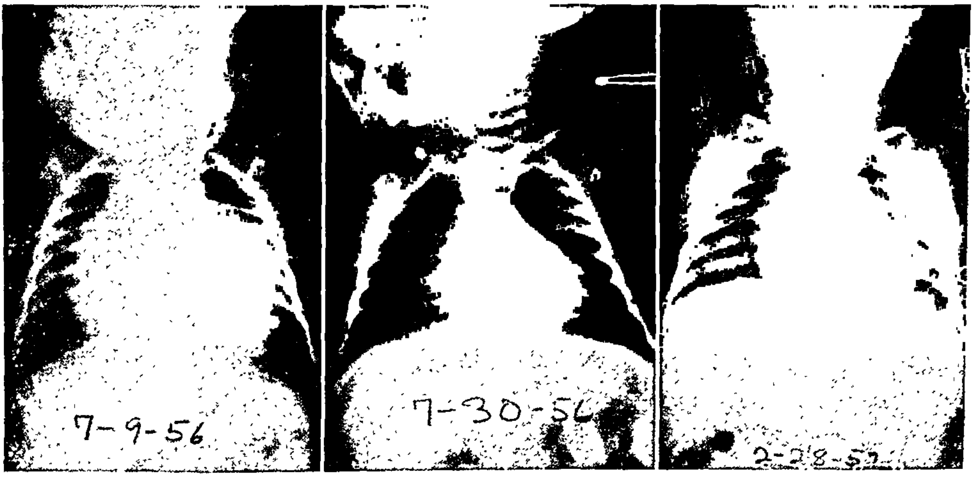
Laboratory examination revealed a red blood count of 6 million and a hemoglobin of 15.3 Gm. (Table I). The white count was 11,600 with 47 per cent neutrophils, 48 per cent lympho-

Table I. Laboratory Data

DATE	R.B.C. (MILLION/ CU.MM.)	HGB. (GM. %)	PBI (µg %)	I^{131} (% UPTAKE)
July, 1956	6.0	15.3		44
September, 1956	3.9	12.5	7.8	45
February, 1957	4.7	11.2		17

cytes, 4 per cent monocytes, and 1 per cent eosinophils. The urinalysis was essentially normal. The nasopharyngeal culture was of no consequence. A lumbar puncture revealed normal spinal fluid, and during the procedure the child became cyanotic, presumably because of pressure of the mass on the airway.

The patient was given an immediate injection of 0.25 ml. of Mercuhydrin intramuscularly, and digitalization was begun. A chest x-ray confirmed the large globular-shaped heart (Fig. 2, *A*), and cardiac fluoroscopy revealed that the pulsations were of a poor quality. Electrocardiogram obtained on the day after digitalis was begun revealed moderate right ventricular hypertrophy. There was no evidence of low voltage or other signs of a myxedematous heart.



A *B.* *C.*

Fig. 2.—Teleorentgenograms of the chest (*A*) on admission, (*B*) three weeks later, and (*C*) seven months later.

Because of these findings it was felt that this patient might have either idiopathic myocarditis or endocardial fibroelastosis, plus a "Roncovite goiter." The child responded well to initial digitalis and oxygen, and no thyroid therapy was begun. Unfortunately, due to a breakdown in equipment, protein-bound iodine studies were not obtained. A bone age was entirely normal, and a radioiodine uptake study done on the fifth day of hospitalization revealed a 44 per cent, twenty-four-hour I^{131} uptake (Table I).

The patient continued to do very well and was discharged after three weeks' hospitalization. A repeat x-ray taken at the time of discharge showed a remarkable change in the size of the heart (Fig. 2, *B*). Two more electrocardiograms taken during hospitalization revealed right ventricular hypertrophy on the basis of a tall R wave in the right chest leads. Since we had no evidence that this child had a myxedematous heart and there was no evidence of hyperthyroidism except on the basis of the iodine uptake, it was felt that digitalization should be continued and the patient should be returned to the hospital for re-examination in approximately one month.

During the interval the child did well and was readmitted to the Children's Hospital five weeks after the first hospitalization. Physical examination was essentially normal. There was no evidence of thyroid gland involvement (Fig. 1, *B*), and he had gained approximately 2 pounds in weight. Chest x-ray at this time was considered probably within normal limits. A repeat I^{131} uptake was 44 per cent in twenty-four hours, and the protein-bound iodine was 6.7 micrograms per cent. The red blood count was 3.9 million and the hemoglobin was 12.5 Gm. per cent (Table I). Urinalysis again was essentially normal. The patient was discharged after the digitalis was discontinued.

The youngster was not seen again until approximately six months later. He was admitted to the hospital for repeat studies. At this time his radioiodine uptake was 17 per cent in twenty-four hours (Table I). Electrocardiogram was considered normal and the child's chest x-ray was normal (Fig. 2, *C*). The hemoglobin at the time of this last admission was 11.2 Gm. and the red blood count was 4.7 million (Table I).

DISCUSSION

This patient raises a number of questions which are very difficult to answer. A relationship between the thyroid goiter and the cardiomegaly is difficult to prove, and the elevation of the radioiodine uptake studies only four days after discontinuance of cobalt therapy deserves comment. The rapidity with which this patient's goiter responded to the simple discontinuance of the use of cobalt leaves little doubt that it was the usually described cobalt goiter. The radioiodine uptake, however, in cases with cobalt goiters are usually normal or low. The explanation for this rather high uptake may be that, following withdrawal of Roncovite and removal of this blocking agent, the hyperplastic thyroid which was in a state of iodine-want, increased its iodine uptake without clinical evidence of hyperthyroidism. Repeat studies six weeks later revealed similar findings but the I^{131} uptake had returned to normal in approximately eight months (Table I). This explanation seems justified by the clinical course.

The cardiomegaly, we felt, was due to pericardial effusion. The clinical evidences were distant muffled sounds on auscultation and poor movements on fluoroscopic study. Electrocardiograms, however, revealed no evidence of a pericardial effusion. Neither did they reveal any evidence of myocarditis, myxedematous changes, or hyperthyroidism. The cardiomegaly may not have been related in any way to the thyroid goiter, but the response of the patient, the return of the cardiac size to normal, and the results of electrocardiographic study are difficult to explain on the basis of myocarditis. This response was so closely related to the discontinuance of Roncovite that the temptation to assume a cause-and-effect relationship is great.

Recently Robey and associates[3] reported a case of a cobalt-induced myxedema. An I^{131} uptake done approximately forty-eight hours after discontinuance of cobalt in this case was 69 per cent. Except for the absence of electrocardiographic signs, our patient would fit all the reported clinical characteristics and may be the second such case.

The patient's general response to discontinuance of cobalt, the return of cardiac size to normal, and a normal electrocardiogram indicate a good prognosis. His weight which was below the sixteenth percentile on the Iowa chart when first seen, is now at the fiftieth percentile. His height has changed similarly.

CONCLUSIONS

1. A case of a presumed cobalt-produced goiter is reported.

2. The relationship between the cardiac failure and the thyroid goiter is discussed.

3. The potential hazard of the indiscriminate use of cobalt in patients in whom iron therapy alone is sufficient is further emphasized.

4. The occurrence of a full fontanel following tetracycline therapy is mentioned. This phenomenon has been observed on several occasions.

5. The relative polycythemia as a result of the cobalt therapy is illustrated.

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TUBERCULOUS MENINGITIS IN CHILDREN TREATED WITH ISONIAZIDMETHANESULFONATE

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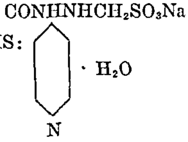
ALTHOUGH the value of isoniazid (INAH) in the treatment of childhood tuberculosis is accepted, it is important to investigate the use of its derivatives. We wish to report on our experience in the treatment of tuberculous meningitis with one derivative, sodium isoniazidmethanesulfonate (IHMS). Previous studies and reports on this derivative have been made by Ceriotti,[1, 2] Logemann,[3] Zamboni,[4] Shimizu,[5] Kitamoto,[6] and Yoshida and associates.[7, 8]

IHMS:



IHMS is a white crystalline powder with a slightly bitter taste. It is 11 to 12 per cent soluble in water at 20° C. On boiling it dissolves into INAH and its dimethansulfonate. It does not combine easily with other substances in vivo, and thus differs from INAH which is apt to acetylize and undergo chemical changes. Its bacteriostatic action in vitro is seemingly somewhat less than that of INAH, but with experimental animals IHMS seems to have a similar or even a little better action. It further has the advantage of lesser toxicity, and hence may be used in larger dosage. Studies of the toxicity made in mice show a toxicity ⅙ to ⅐ that of INAH.

In addition to its clinical use in ten cases of severe tuberculous meningitis discussed below, studies were made (1) of its hemolytic action in vitro, and (2) of its concentration in the blood and cerebrospinal fluid.

1. The hemolytic action of IHMS in vitro is shown in Table I. No hemolysis occurred in cerebrospinal fluid added to IHMS, whether at 37° C. or 10° C., after a period of 24 hours.

2. Ninety-nine determinations were made of the concentration in the blood

TABLE I. HEMOLYTIC ACTION OF IHMS IN VITRO (37° C., 2 HOURS)

IHMS (%)		0	0.25	0.5	1.0	2.0	4.0	8.0
NaCl (%)	0	++++	+++	+++	+++	+	–	–
	0.2	+++	+++	+++	++	–	–	–
	0.3	+++	+++	++	–	–	–	–
	0.4	+	±	–	–	–	–	–
	0.5	–	–	–	–	–	–	–
	0.6	–	–	–	–	–	–	–
	0.8	–	–	–	–	–	–	–
	IHMS (%)	0	0.32	0.63	1.25	2.5	5.0	10.0
Cerebrospinal fluid		–	–	–	–	–	–	–

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and cerebrospinal fluid electrophotometrically, using 1-2 naphtochinondisulonacidsodium.[9] A comparison between *the blood concentration* following oral administration of IHMS and INAH in a dosage of 10/mg./kg. is shown in Fig. 1.

The blood concentration was determined after the administration of larger doses of IHMS (17/mg./kg. and 50/mg./kg.). The concentration increased, paralleling the dosage, but after 24 hours the concentration was low in every instance, averaging around 0.3γ/c.c.

In two patients without symptoms of meningitis the concentration was 0.7 and 0.8γ/c.c. after 3 hours, 1.1γ/c.c. after 6 hours, and 0 and a trace after 24 hours.

CLINICAL STUDIES

After first trying the effect of IHMS in a patient who was not improving on INAH, the study was extended to include 10 cases of tuberculous meningitis. All were severe cases and presented factors disadvantages to therapy.

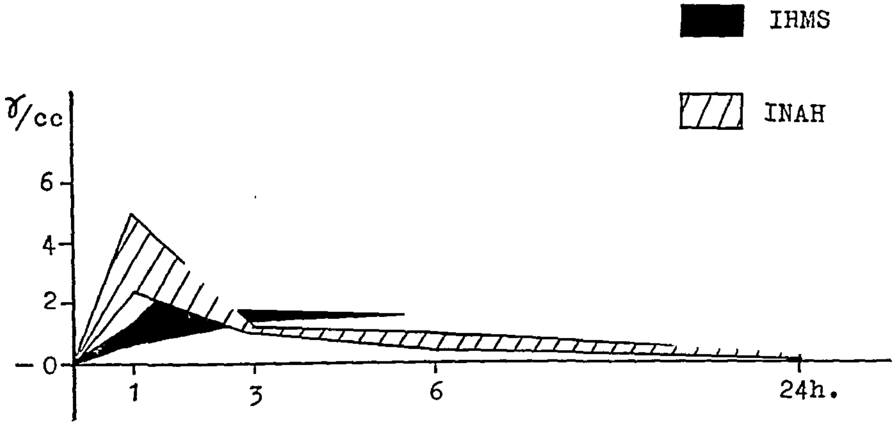

Fig. 1.—Blood concentration of IHMS and INAH after oral administration (dosage of each, 10 mg./Kg.)

Comparison of the blood concentration following intramuscular injection of 10/mg./Kg. with oral administration is shown in Fig. 2.

Studies were made of the concentration in the cerebrospinal fluid following the oral administration of 10/mg./Kg.

The values found in two patients in the recovery stage of tuberculous meningitis were 0.3γ/c.c. after 1 hour, 1.0γ/c.c. and 1.4γ/c.c. after 3 hours, 2.1γ/c.c. after 6 hours, and 0 and a trace at the end of 24 hours.

a. In 5 cases (Cases 1, 6, 7, 9, 10) there was moderate or deep unconsciousness.

b. In 4 cases (Cases 1, 6, 7, 9) treatment had been delayed.

c. In 4 cases (Cases 2, 3, 7, 9) including 3 with recurrent meningitis, there had been previous chemotherapy.

d. In 1 case (Case 4) there was a prolonged clinical course despite streptomycin (SM) and INAH therapy.

The following plan of administration of IHMS was followed. Maximum dosage was reached in a few days and continued until improvement, when the dosage was either decreased or given at two-day intervals. The maximum was 30-49 mg./Kg. in 4 cases, and 50-160 mg/Kg. in 6. The duration of the treatment in the individual cases is shown in Table II. In addition, as most of the cases were severe, other chemotherapeutic drugs were combined—streptomycin (0.25-0.5 Gm./day intramuscularly, and 20-50 mg./day intrathecally, and PAS, about 0.2 Gm./Kg./day) orally. The total dosage of streptomycin was 0-14 Gm. in 7 patients and 15-30 Gm. in three.

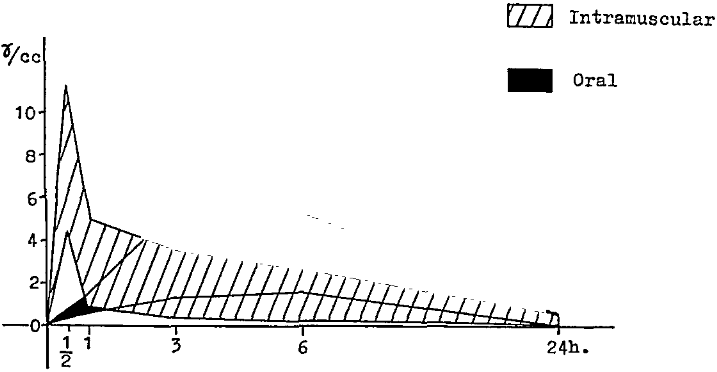

Fig. 2.—Blood concentration of IHMS after intramuscular administration compared with that after oral administration (dosage, 10 mg./Kg.)

The clinical results are summarized in Table II. Seven were cured and three died. In one case (Case 10) slight motor paralysis remained after treatment. Five of the 7 cases have been followed for more than 20 months without relapse. Two of the 3 deaths occurred shortly after the beginning of treatment with IHMS (22 hours and 28 days, respectively), and one patient died more than a year later following the development of encephalitic symptoms which led to the stopping of chemotherapy. In 3 cases ACTH was also used (10-20 units for 1-3 weeks) but no aggravation of the tuberculous lesions due to the use of ACTH could be found.

Brief reports of 4 of the cases are given here.

Case 1.—T. K., aged 2 years and 6 months, was admitted on the thirty-second day of illness. She was somnolent, with left hemiparesis. Nutrition was poor and weight was 7.8 Kg. (78 per cent of standard). Treatment was started with SM (both intramuscularly and intrathecally), PAS, and IHMS in ordinary dosage. At first, slight improvement took place, but on about the 40th day of treatment the condition worsened, and by the 50th she was entirely apathetic. As the general condition was gradually deteriorating, the dosage of IHMS was increased on the 96th day, reaching 160 mg./Kg./day by the 105th day. Of this, 100 mg. was given orally, 50 mg. intramuscularly, and 10 mg. intrathe-

CASE	AGE AND SEX	DOSAGE				DURATION OF MORE THAN 30 MG./KG.	DURATION OF TOTAL TREATMENT				PERIOD OF OBSERVATION
		DAYS AFTER OUTBREAK OF ILLNESS	UNCONSCIOUSNESS AND OTHER CONDITIONS	MAXIMUM DOSAGE (MG./KG.)	DURATION			FEVER NORMALIZED FROM APPROX. DAY	NUMBER OF LEUKOCYTES IN CEREBROSPINAL FLUID	RESULTS	
1	2 yr. 6 mo. (♀)	40	+ + (Left hemiparesis)	160	At first 14 days; afterward, 8 days	6 mo.	12 mo.	200th	Less than 16 per c.mm. from 246th day	Cured	1 yr., 8 mo.
2	5 yr. 8 mo. (♀)	10	±	40	75 days	8 mo.	1 yr., 6 mo.	85th	Less than 16 per c.mm. from 106th day	Cured	2 yr., 7 mo.
3	3 yr. 4 mo. (♂)	28	–	59	70 days	12 mo.; 4 mo.	1 yr., 8 mo.	200th	Less than 16 per c.mm. from 189th day	Cured	2 yr., 8 mo.
4	1 yr. 9 mo. (♂)	60	– (No tendency to healing after INAH, SM, PAS treatment)	32	57 days	3 weeks × 2; 1 mo. × 1	1 yr., 4 mo.	180th	Less than 16 per c.mm. from 170th day	Cured	2 yr., 4 mo.
5	6 yr. 11 mo. (♂)	36	–	43	140 days	4 mo.	1 yr., 6 mo.	185th	Less than 16 per c.mm. from 129th day	Cured	1 yr., 9 mo.
6	5 yr. 10 mo. (♂)	27	+ + + (Left hemiparesis)	70	10 days	7 mo.	8 mo.	Temporarily improved; during treatment encephalitic symptoms aggravated; chemotherapy stopped		Died	1 yr., 3 mo.
7	5 yr. 4 mo. (♀)	21	+ + + (Right hemiparesis)	76	⅔ day	⅔ day	⅔ day	Removed in lethal condition. No effect		Died	22 hours
8	9 yr. 5 mo. (♀)	43	–	30	9 weeks; 3 weeks	4 mo.	12 mo.	128th	Less than 16 per c.mm. from 180th day	Cured	12 mo.
9	3 yr. 6 mo. (♂)	39	+ + +	67	10 days	10 days	13 days	Took large doses of IHMS with ACTH. Fever temporarily alleviated; consciousness recovered; afterward aggravated		Died	28 days
10	1 yr. 11 mo. (♂)	34	+ + (Right hemiparesis)	50	3 weeks; 9 weeks	1 mo.; 2 mo.	6 mo.	180th	Less than 24 per c.mm. from 148th day	Cured	10 mo.

cally. Improvement was rapid. The intermittent type of fever which had been reaching 39.5°-40° C. fell to 36.8°-38° C. from the 109th day. Her silence, which had lasted for 40 days, was broken, and her condition took a favorable turn. Complete recovery took place without residuals. The spinal fluid leukocyte count on the 32nd day of the illness was 766. On the 135th day it had fallen to 81, and was less than 20 after the 246th day.

Case 2.—S. M., aged 5 years and 8 months, had been treated by one of us (H. Y.) three years previously for tuberculous meningitis with SM and PAS, and the present illness was a relapse. IHMS was given orally in a dosage of 40 mg./Kg./day for the first 75 days followed by 30 mg./Kg./day for 6 months. After the 85th day the temperature became normal and improvement in the blood sedimentation rate and in the cerebrospinal fluid took place. After 4 months in the hospital she was discharged in good condition.

Case 4.—S. N., aged 1 year and 9 months, was treated for 2 months with INAH and PAS orally, combined with SM intramuscularly. The remittent fever continued and the leukocyte count in the spinal fluid was 377. On the 60th day the INAH (8 mg./Kg.) was changed to IHMS (32 mg./Kg.). Improvement followed and the temperature remained normal after the 108th day. He was discharged completely well.

Case 9.—T. M., aged 3 years and 6 months, was treated with SM, PAS, and IHMS beginning with the 35th day of illness. At first there seemed to be a slight improvement, but the condition soon became worse and encephalitic symptoms developed. Death occurred on the 28th day of treatment.

COMMENT

Although children are regarded as having a better tolerance to INAH than adults, the usual dosage is 8-10 mg./Kg./day. Kleinschmidt[10] has reported liver damage when more than 10 mg. per day was given. Preliminary studies of the hemolytic action of IHMS, and of the blood and spinal fluid concentrations, led to our considering its clinical use. While the concentration in the blood was slower in developing than with INAH, the maximum concentration was almost the same for the two drugs. Furthermore, a high concentration lasted longer with IHMS. The maximum concentration was reached more rapidly when IHMS was given intramuscularly, but fell more rapidly than took place with oral administration. An active diffusion into the cerebrospinal fluid took place even in normal children.

With these preliminary findings as a basis, the clinical use of IHMS in the treatment of tuberculous meningitis was started. The patients were followed with liver function tests (Bromsulphalein, serum bilirubin reaction, serum sublimate reaction, santonin test, and urinary urobilinogen) as well as the blood picture and bleeding time. Nothing was found which was considered as due to the treatment. But we have seen some evidences of liver function damage in the long-term use of large doses of IHMS in the treatment of chronic pulmonary tuberculosis in adolescents.[11] Recently we have been using ACTH in combination with IHMS without evidence of any aggravation of the tuberculous lesions. Taking into consideration the severity of the cases of tuberculous meningitis in which the drug was used, we feel that it was very effective when given in large dosage. The reasons for this are probably the high and persistent blood concentration, together with its good diffusion into the cerebrospinal fluid.

SUMMARY

Isoniazidmethanesulfonate, a derivative of INAH, was used in the treatment of ten children with severe tuberculous meningitis. The clinical results were favorable, and we believe it warrants further trial.

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*Other articles from the Japanese literature are available on request to the author.

Some Pertinent Advice for Pediatricians

With regard to the exhibition of drugs as a part of your medical treatment, the golden rule is, *be sparing.* Many remedies you give would make a well person so ill that he would send for you at once if he had taken one of your doses accidentally. It is not quite fair to give such things to a sick man, unless it is clear that they will do more good than the very considerable harm you know they will cause. Be very gracious with children especially. I have seen old men shiver at the recollection of the rhubarb and jalap of infancy. You may depend upon it that half the success of Homoeopathy is due to the sweet peace it has brought into the nursery. Between the gurgling down of loathsome mixtures and the saccharine deliquescence of a minute globule, what tender mother could for a moment hesitate?

FROM AN ADDRESS BY OLIVER WENDELL HOLMES, M.D., DELIVERED IN 1858 TO THE MEDICAL GRADUATES OF HARVARD UNIVERSITY, THE BOSTON MEDICAL AND SURGICAL JOURNAL

WHIRLING AS A CLINICAL TEST IN CHILDHOOD SCHIZOPHRENIA

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THE "whirling" response or test has been described as highly specific for childhood schizophrenia.[1] The test is performed as follows:[1, 2] The child stands with his arms extended, parallel to each other, and with his eyes closed (Fig. 1, *A*). In order that he may be distracted, he is asked to count. The head is now passively rotated to one side as far as possible without discomfort. Reaction is noted and the head is rotated to the other side. The positive response, or whirling, consists of the child's turning his entire body as long as the examiner turns his head (Fig. 1, *B*). The negative response consists of a slight rotation of the trunk but the entire body does not turn (Fig. 1, *C*).

Although the validity and reliability of the whirling test have never been demonstrated, the test is presented in the literature[1-10] not only as a diagnostic aid but as a characteristic sign of childhood schizophrenia. Furthermore, the test has been offered as important evidence for the "maturational lag" concept of childhood schizophrenia.[6, 8, 11]

The purpose of this investigation was to ascertain the value of the whirling test as a diagnostic aid and as confirmatory evidence for the maturational lag concept of childhood schizophrenia. This will be done by (1) reviewing the proposed clinical significance and physiological basis of whirling and its use as evidence for the maturational lag concept of childhood schizophrenia and (2) comparing the incidence of whirling in a group of normal children with the incidence in a group of children with the diagnosis of schizophrenia.

WHIRLING

Clinical Significance.—Bender[1] and Silver[2] stated that the whirling response is normal up to the age of 6 and that its persistence beyond that age indicates an abnormal condition. Teicher,[12] studying children with behavioral problems, indicated that the response is normal up to the age of 8 years.

Bender[1] regarded the test as highly specific for childhood schizophrenia after the age of 6. She[1] added, however, that it is a very sensitive test procedure for many types of motor disabilities in children. Silver[2, 4] stated that whirling after the age of 6 is seen in childhood schizophrenia, cerebral damage, and reading disabilities. Teicher[12] regarded its persistence after the age of 8 as a pathological response indicating general retardation or organic brain damage.

Physiological Basis.—Both the tonic neck reflex and the neck-righting reflex* have been said to constitute the physiological basis of the whirling phenomenon.

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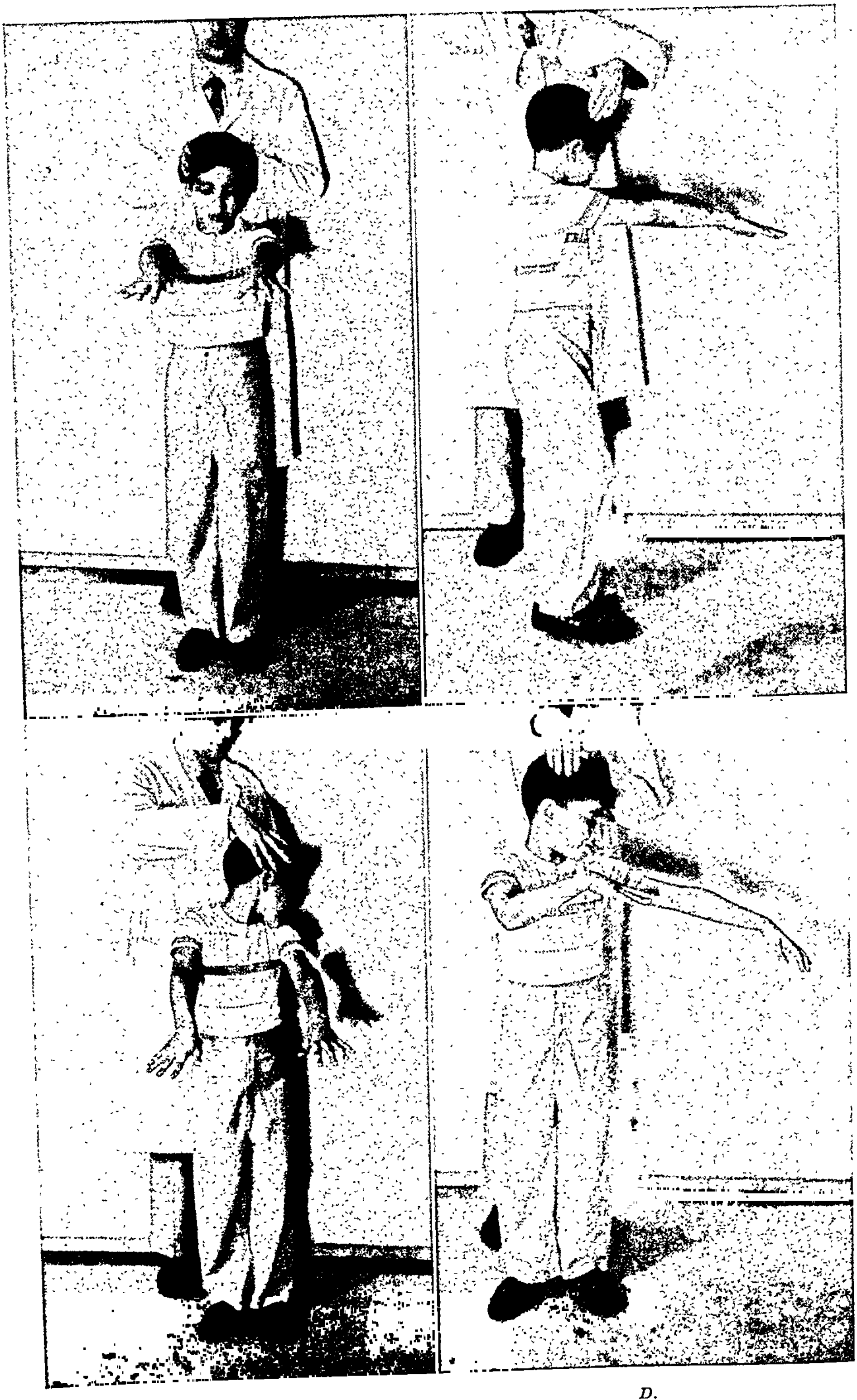
*Both the specificity and the classical reflex character of many of the Magnus "reflexes" have been questioned by Kurt Goldstein.[13]



A.

C.

D.

Fig. 1.—"Whirling" test. *A*, Starting position. *B*, Positive response or whirling." *C*, Negative response. *D*, Classical tonic neck position.

Although not specifically stated, it is implied that the classical tonic neck reflex (Fig. 1 *D*) is commonly seen in schizophenic children during the whirling test[2, 14] and this belief has apparently been used as evidence for the concept that the physiological basis of the whirling test is the tonic neck reflex.[5, 6, 8, 10, 15] Bender has stated repeatedly [5, 6, 10, 15] that the whirling response is based on, or is, a primitive tonic neck postural reflex.

The neck-righting reflex was described in animals by Magnus[16] as one of the many postural reflexes which permit an animal to assume and maintain an upright posture. The reflex orients the body in relation to the head. If the head of an animal is turned to the side the body will rotate to bring it to symmetrical alignment with the head. Schaltenbrand,[17] in 1925, was the first to attempt to elicit the neck-righting reflex in human infants and assumed that the response was the same as that described in animals by Magnus. Schaltenbrand stated further that the response normally disappears at about 5 years of age. (Schaltenbrand's work is discussed more fully elsewhere.[18])

Because of the gross similarity between Schaltenbrand's neck-righting reflex in infants and the whirling phenomenon, both Schilder[19] and Silver[2] assumed that the neck-righting reflex is the basis of the whirling phenomenon.

Whirling as Evidence for the Maturational Lag Concept of Schizophrenia.—In 1952 Bender[6] presented her concept of childhood schizophrenia as a "developmental lag at the embryological level, characterized by embryonic plasticity of the biological processes. . . . The biological areas are best defined according to Gesell's concepts describing *The Embryology of Behavior,* namely, homeostatic mechanisms, tonic-neck reflex motor patterning, muscular tone, respiratory patterns, and waking and sleeping with changing states of consciousness."

This theory postulates that childhood schizophrenia is the result of the failure of certain "biological processes" to mature. The schizophrenic child, in the areas mentioned above, is at a stage of development characteristic of the normal fetus. The psychological characteristics of schizophrenia are secondary to this lag in development. The persistence of the whirling response above the age of 6 is a manifestation of immaturity in one of these biological areas: tonic neck reflex motor patterning.

According to Bender there are manifestations of immaturity in the other biological areas outlined by Gesell: soft "doughy" musculature, poor homeostatic control, abnormal speech-respiratory patterns, etc. But whirling is the most accessible to investigation and its presence in a child is readily determined, whereas the presence of many of the other signs of immaturity are difficult to evaluate objectively. Moreover, Bender[6] regarded whirling as one of the most important confirmations of her theory.

WHIRLING IN FOUR GROUPS OF CHILDREN

Subjects and Methods.—The first group consisted of 266 white children from middle-income families. They were from 6 to 11 years old and attended two public schools in Roselle, New Jersey. The second group consisted of 244 Negro children from lower-income families. They were from 5 to 11 years old and attended a large public school in the Harlem section of New York City. All of the children in the middle-income white population were tested; the regular classes in the lower-income Negro population were randomly sampled.

The third and fourth groups tested were 44 children at Bellevue Hospital and 71 children at Rockland State Hospital, all of whom had had diagnoses of childhood schizophrenia. Bellevue, in attempting to detect less obvious cases of childhood schizophrenia, employs somewhat different diagnostic criteria, and, partly for this reason, its children appeared less disturbed than those at Rockland, many of whom were autistic, and the great majority of whom were obviously psychotic. This is disclosed by the fact that of the 71 children at Rockland only 48 could comply with the test, whereas all of the Bellevue children were in sufficient contact to perform the test adequately. Almost all of the children at Bellevue and an indeterminate number at Rockland had been tested previously. The children were from 6 to 11 years old and were from varied backgrounds.

The children were examined separately and in such a way that no child could have any knowledge of the test beforehand or view any other child taking the test. The test was performed as described above (Fig. 1). Some of the children will continue to rotate or whirl when the head is no longer being turned. This variety of response was designated as "continual whirling" and, as it may be interpreted to represent a more extreme positive response than the usual whirling response, in which the child will stop moving when the head is no longer being turned, this phenomenon was noted when present. In the tabulation of the results, the positives will include both varieties of whirling. Observations were also made for the presence of the classical tonic neck reflex (Fig. 1, *D*).

TABLE I

AGE (YEARS)	NO. TESTED	POSITIVE		NO. TESTED	POSITIVE	
		NO.	%		NO.	%
		A. Whirling in Normal Children				
Middle-income Whites.—				*Lower-income Negroes.—*		
5	–	–		32	28	88
6	26	13	50	35	29	83
7	61	31	51	33	24	73
8	41	18	44	36	23	64
9	52	25	48	37	24	65
10	46	15	33	30	13	43
11	40	4	10	41	14	34
		B. Whirling in Schizophrenic Children				
Bellevue.—				*Rockland.—*		
6	–	–		3	3	100
7	6	5	83	4	4	100
8	10	7	70	9	8	89
9	13	9	69	11	10	91
10	7	4	57	12	8	75
11	8	2	25	9	5	56

C. Continual Whirling

	MIDDLE-INCOME WHITES	LOWER-INCOME NEGROES	BELLEVUE SCHIZOPHRENICS	ROCKLAND SCHIZOPHRENICS
Number tested	266	244	44	48
Number positive	8 (3%)	57 (23%)	15 (34%)	22 (46%)

Results.—

Whirling: The results are shown in Table I and Fig. 2. The Rockland schizophrenics had the highest and the middle-income whites the lowest incidence of whirling at every age level tested. These two groups were each significantly different from the two other groups tested and from each other.* Between these two extremes were the Bellevue schizophrenics and the lower-income Negroes. Although the Bellevue schizophrenics were slightly higher than the lower-income Negroes in the sample of the size tested, the difference is not significant.

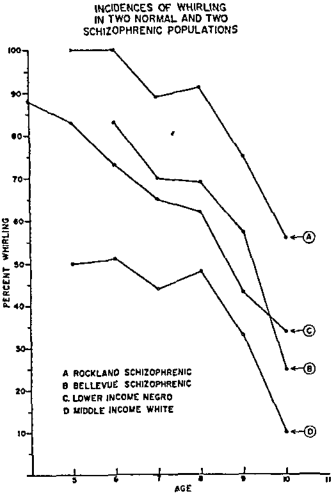


Fig. 2.

There is evidence to suggest that the different incidence of whirling in these two normal groups is not a simple function of race and may be explained in part, at least, by the influence of environmental factors: the incidence of whirling in 53 7-year-old and 49 11-year-old Negro children who were in a higher socioeconomic group than the lower-income Negro children was 51 per cent and 55 per cent, respectively. This is significantly different from the incidence in the corresponding ages in the lower-income Negro population.

There was no significant difference between the incidences of whirling in boys and girls within any of the groups tested.

Continual whirling: Continual whirling was reported in terms of the whole group tested because there was no age trend. The incidence of continual whirling was significantly higher in the lower-income Negroes than in the middle-income whites. The incidence of continual whirling was highest in the two schizophrenic groups but no significance can be attributed to the incidence of continual whirling in these groups because many of the children had been tested previously. (A study of the effect of repeated testing in 47 children disclosed that a child who does not whirl initially will not generally whirl on repeated testing and the converse. However, almost one third of the children who whirl initially will on being tested once or twice more whirl with greater ease and will whirl continually. Continual whirling, therefore, is only a reliable index of the ease of whirling when the child has never been tested previously.

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*The level of significance used throughout this paper is 5 per cent. The method used in comparing the incidence of whirling in the groups as a whole is the sign test because of the small size of the sample in each age group. All other comparisons are made using chi square.

Tonic neck reflex: None of the children in any group showed an unambiguous tonic neck reflex posture. Of the 92 schizophrenic children, 4 showed a posture which slightly resembled a tonic neck reflex; such postures were also seen in the normal groups during performance of the whirling test.

RELATION OF WHIRLING TO NECK-RIGHTING OR TONIC NECK REFLEX

The purpose of this study was to determine whether the same response, i.e., rotation of the body, as seen when the head is turned, could be induced by a completely different stimulus which has nothing to do with head rotation or position.

One crucial modification of the whirling test was made. The child was given identical instructions and began, as in whirling, with his arms outstretched, his eyes closed, and counting aloud. Then instead of turning the head, the examiner grasped the last digit of the middle finger of one hand and drew the arm laterally in an arc to the left side if the left arm was used, or to the right side if the right arm was used. As in the whirling study the child was observed for body rotation.

In this test we were interested in two questions: whether the incidence of whirling—that is, body rotation induced by head turning—would be similar to the incidence of body rotation induced by arm abduction; and also, whether a given child would respond in a similar way to both stimuli.

These tests were done on a group of Negro children from middle-income families.

The first question, whether the incidence of body rotation induced by head turning would be similar to that of body rotation induced by arm abduction was studied in two sixth-grade classes which together had a total of 49 students. Most of the children were 11-year-olds. On a random basis, half of the children, 25, were tested by head turning, and half, 24, by arm abduction.

The second question, whether a given child would respond in a similar way to both stimuli, was tested in two second-grade classes which together had a total of 53 students. Most of the children were 7-year-olds. Each child was tested by both head rotation and arm abduction. Half of the children, 27, were randomly picked to begin with head rotation followed by arm abduction; the other half, 26, with arm abduction followed by head rotation.

Results.—The results may be seen in Table II. The incidence of body rotation induced by head turning was

TABLE II. BODY ROTATION INDUCED BY HEAD TURNING AND ARM ABDUCTION

A. 49 Sixth-grade Children, Either Arm Abducted or Head Rotated in Each Child

RESPONSE	HEAD ROTATION	ARM ABDUCTION
Positive	14 (56%)	14 (58%)
Negative	11	10
Total tested	25	24

B. 53 Second-grade Children, Arm Abducted and Head Rotated in Each Child

RESPONSE		
Negative to both procedures	23	
Positive to both procedures	27	
Total either positive or negative to both	50	(94%)
No. responding differently to arm and head	8	(6%)
Total tested	53	

practically identical with the incidence of body rotation induced by arm abduction. Furthermore, a given child generally responded to both procedures in an identical manner.

Thus the response of body rotation can be induced by a stimulus which has nothing to do with that used in eliciting neck-righting or tonic neck reflexes. The response of whirling, therefore, may have nothing to do with these reflexes, which are generally considered to be specific postural responses determined by head position.

DISCUSSION

Several characteristics of the whirling response make it difficult to conceive of it as a reflex in the classical sense; the whirling response shows great variability between individuals, the stimulus is nonspecific, the latent period is long, there is voluntary control over the response, and repeated testing commonly alters the response.

Whirling is a complicated phenomenon and one can only speculate as to why one child whirls and another does not. Some of these factors may be:

1. General patterns of compliance; a more compliant child may permit his body to be rotated. It was our impression from observing the behavior of the children in the normal groups that this may be one of the most important factors and may partly explain the difference between the Negro children from low-income families and the white children from middle-income families.
2. The child's conscious conception of what he is expected to do; this may depend upon his having seen the test performed on another child or having heard about the test. It may be a kind of projective test in which the child transfers his own attitudes toward authority into the test situation.
3. General postural patterns; a child with a more malleable or adaptable posture may whirl more readily than one with a stiff or rigid posture.
4. Enjoyment of rotational movement; a child who enjoys the sensation of rotating his body may be more likely to whirl.
5. A younger child is generally more likely to whirl. This is probably due to a change in the relative strength of some of the foregoing factors which comes with increasing age.

Several conclusions can be made concerning the whirling response:

1. It is affected by many factors.
2. The same response can be induced by stimuli not connected with neck or head position.
3. It is probably not based on the tonic neck or neck-righting reflex and probably is not itself a reflex.
4. The response, when present, frequently is more easily induced with repeated testing.

5. It is commonly seen in normal children between the ages of 6 and 11, and with decreasing frequency as the age increases.

6. It is commonly although not universally seen in schizophrenic children between the ages of 6 and 11. It is not accompanied by the classical tonic neck reflex.

7. The incidence of whirling appears to be significantly higher in a group of obviously psychotic schizophrenic children (at Rockland State Hospital) than in any normal group of children. In a group of children with the diagnoses of schizophrenia (at Bellevue Hospital), in whom an attempt was made to detect less obvious cases of abnormality, the incidence is slightly but not significantly higher than in a normal lower-income Negro group.

8. The whirling test cannot be employed as a diagnostic sign of mental disease because of the large number of children with mental disease who do not whirl.

9. The whirling response cannot be used as evidence in support of the maturational lag concept of childhood schizophrenia because normal children over 6 years of age commonly exhibit this phenomenon and because there is no evidence that whirling is based on primitive tonic neck reflex patterns.

In view of these considerations, it appears that with our present state of knowledge the whirling test is not a useful test in child psychiatry.

SUMMARY

"Whirling" is a postural test in which the head is turned and the body follows the rotation of the head. It has been claimed that a positive response in a child over the age of 6 indicates mental disease, particularly childhood schizophrenia. In an attempt to evaluate this test, over 700 normal and schizophrenic children were tested. The incidence of whirling in both groups was found to be so high that the test could not be used in establishing a psychiatric diagnosis. The use of the test as evidence in support of the maturational lag theory of childhood schizophrenia is discussed.

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The Health of St. Louis in 1858

The high water of the spring, followed by the extreme heat of the summer, have given rise to an unusual amount of intermittent and remittent disease during the present season, especially in the outskirts and environs of the city. During the hot weather of the latter part of July, and the beginning of August, quite a number of deaths occurred from sunstroke, principally among the intemperate and exposed; the same cause also gave rise to an increased mortality among young children during the same period.

Our hospitals, too, have been well filled with patients, and occasionally a death has taken place from yellow fever imported from New Orleans, but in no instance has this disease originated here, nor spread when introduced into a crowded ward—showing most conclusively its non-contagiousness.

From the St. Louis Medical and Surgical Journal.

CANNULA-SWAB TECHNIQUE FOR OBTAINING VAGINAL SECRETIONS PAINLESSLY IN YOUNG GIRLS

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BAKERSFIELD, CALIF.

VAGINITIS in the very young female and prepubescent child is often a source of greater concern to patient and family than it is to the physician. For this reason and because it is important to relieve the mind of the parent as well as to identify if possible the offending organism or foreign body, the simplest and least painful method for securing vaginal material should be employed.

To those who deal with many young females it is common knowledge that the most cooperative child or preteen-ager will become apprehensive at any manipulation in or about the vulva. The insertion of even the thinnest cotton-tipped applicator beyond an introitus that is either small or inflamed or both causes the child pain and irritation great enough to make further examination an unpleasant struggle, not to mention the attendant physical as well as psychological trauma.

On the other hand, it has been my experience that upon proper explanation and reassurance a small sterile metal cannula of medium caliber (14 F.) can readily be inserted into a vaginal orifice of any size with little or no resistance upon the part of the patient. To recover enough secretion, however, even with the aid of a suction bulb, to make a satisfactory smear, culture, or wet mount is difficult when a simple metal catheter is used alone.

The following unit was devised to permit painless and easy insertion of a curved metal No. 14 F. cannula, the end of which is open, round, smooth, and dull. A thin flexible metal applicator with roughened tip to prevent cotton from sliding off in the vagina is then inserted into the cannula and the entire unit autoclaved in that manner. When ready for use, the cannula is readily inserted without lubrication into the smallest vaginal orifice, detecting by contact any hard foreign body such as a hairpin, marble, metal ball, etc. The cannula is then withdrawn to a spot about midway in the vault and the cotton-tipped applicator is gently pushed out to a distance of not more than 2 cm. beyond the end of the cannula, as indicated by a marker on the handle of the applicator which extends well outside the vaginal orifice.

The unit is then rotated in the vault and slowly withdrawn to pick up secretions. The applicator having trapped specimens of the vaginal contents on the way, out can then be used for smear, culture, or wet mount; moreover, it can readily be changed into an irrigating cannula if larger amounts of vaginal secretions for cytological or other purposes are desired (i.e., sex chromosome studies). What is more

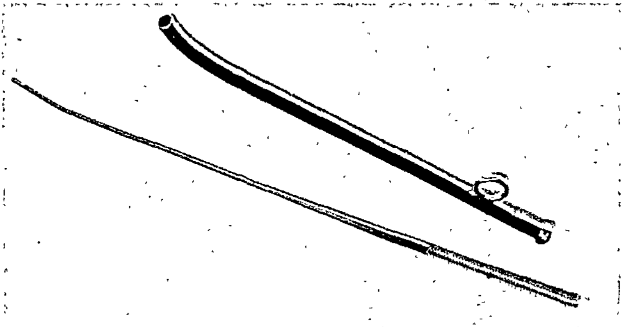

Fig. 1.

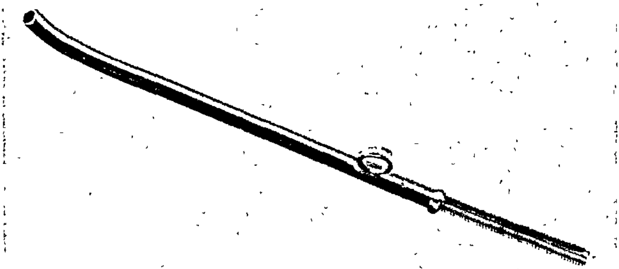

Fig. 2.

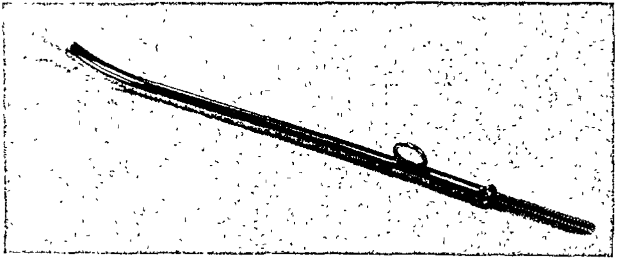

Fig. 3.

Fig. 1.—Unit disassembled, showing cannula and metal applicator with marker on handle.

Fig. 2.—Units assembled, autoclaved, and ready for insertion into vaginal orifice. Cotton-tipped applicator well shielded by metal cannula.

Fig. 3.—Cannula in position within vaginal vault and applicator pushed out beyond cannula tip to a point indicated on handle of applicator. Swab readily rotated with cannula in vault. Unit then withdrawn in this position.

important, however, is that the entire procedure is painless and simple and spares the child a traumatized vulva as well as an unhappy experience.

PURPOSE

The purpose of this type of unit is to avoid the customary pain experienced by most apprehensive little girls undergoing vaginal inspection when even small dry cotton swabs are introduced carefully into a small introitus. Both physical and psychic trauma is great.

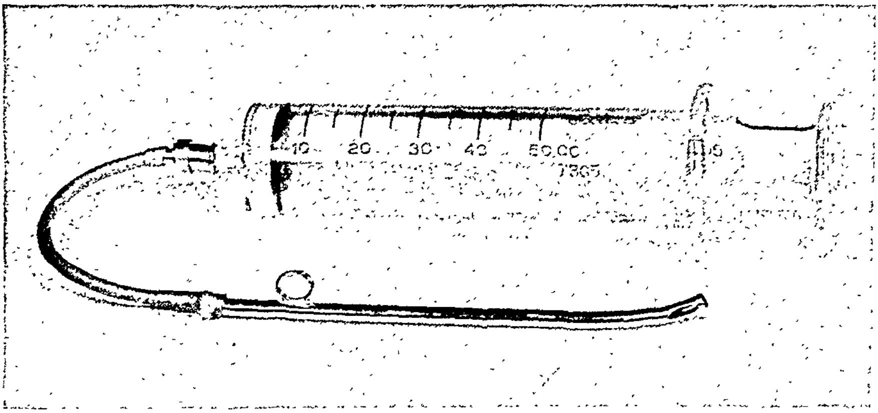

Fig. 4.—Instrument arranged for either suction of vaginal contents or irrigation of the vault.

DESIGN

The metal cannula (Fig. 1) is chrome plated, about 7 inches long, and open at both ends with a slight upward curve at the distal end, size 14 F. There is an "eye" on one side to facilitate painless suction. The flexible metal cotton applicator has a rough tip to secure the cotton and prevent its coming off during manipulation. There is a mark on the handle of the applicator to indicate the distance past which the applicator should not be pushed when in the vagina. The applicator with the cotton tip is set into the cannula (Fig. 2) prior to autoclaving with the cotton not protruding.

METHOD OF USE

The child is shown that the cannula is small, cool, smooth, and painless, and when she is reasonably reassured it is then gently inserted past the vaginal orifice with minimal lubrication. The cannula acts as a painless guide and casing over the cotton tip which is in place but not presenting. The operator gently inserts the cannula into the vagina, feeling for any hard foreign objects in passing. When the cannula is "set," the handle of the applicator is gently pushed past the distal end of the cannula (Fig. 3) to a point not farther than is indicated by the marker on the handle. The unit is then rotated and withdrawn to secure recovery of as much secretion as possible. The unit is then placed in a sterile test tube for laboratory examination. The unit can also be set up for suction and/or irrigation of the vagina if desired (Fig. 4).

CURRENT MANAGEMENT OF STRABISMUS IN CHILDHOOD

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THE pediatrician is immediately consulted for confirmation and advice when a parent, friend, or relative observes malalignment of a child's eyes. Strabismus is a challenging subject, but continuous research and study have brought to light new ophthalmological concepts which are gradually becoming standard procedures.

It has been estimated that 2.7 per cent of children have some form of strabismus.[6] This field, therefore, offers a prime opportunity to practice preventive medicine in the following ways: (1) prevention of the development of amblyopia (failure to develop normal visual acuity in an otherwise normal eye); (2) stimulation of the normal development of fusion (simultaneous use of the two eyes with some degree of depth perception); (3) prevention of psychological problems resulting from cosmetic defects.

The first question to be answered is, "Does the child actually have strabismus?" The average infant develops coordinated eye movements by the end of the third month. The limit of incoordinate ocular movements is about the eighth month. Diagnosis must differentiate it from pseudostrabismus, i.e., epicanthi, narrow interpupillary distance, and negative angle Kappa.[7] A phoria (tendency to deviate from parallelism only when fusion is suspended) must be differentiated from a tropia (deviation present at all times, the fusional reflexes having failed to maintain proper alignment).

The next question is, "Which eye deviates?" There are two classifications: monocular, in which the same eye constantly deviates; and alternating, in which either eye may deviate while the contralateral eye is used to fix the object of regard. This differentiation is of vital importance. It is in the group of monocular strabismus that serious uniocular defects occur and must be recognized in order to determine accurately the final prognosis. An immediate and thorough fundus study of each eye must be performed on a child with strabismus while the pupils are widely dilated. The important pathological processes to be considered are: (1) congenital infections such as syphilis, tuberculosis, and especially toxoplasmosis, which result in destruction of the choroid and overlying retina, particularly in the macular area, destroying potential central vision; (2) congenital malformations of the eye which interfere with the development of vision, i.e., cataract, colobomas, aplasia, and congenital glaucoma; (3) arrested stages of retrolental fibroplasia, which must be ruled out in premature infants, especially where oxygen has been used; (4) the possibility, which is of prime

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importance, that monocular strabismus may be the first sign of an intraocular tumor, especially retinoblastoma; (5) the presence of grossly unequal refractive errors (anisometropia) which prevent the simultaneous perception of similar-sized images on the retina. Any of these conditions alter the prognosis for a lasting cosmetic and functional result. Monocular squinters usually develop amblyopia ex anopsia in the deviating eye. Since the squinting eye receives a different retinal image from that of the fellow eye, diplopia ensues. In young infants, diplopia should be considered, even if strabismus is not obviously apparent, when a head tilt is observed, if one eye is kept closed, or if the child is awkward, stumbles, falls, or overreaches. To prevent confusion, the image of the deviating eye is suppressed and vision does not develop normally in this eye. The amblyopia is the result and not the cause of the squint. The sequence for development of normal distance visual acuity is as follows: 1 year, 20/100 (6/30); 2 years, 20/70 (6/20); 3 years, 20/40 (6/12); 4 years, 20/30 (6/9); and by the fifth year, 20/20 (6/6). Thus an eye which deviates early has a more profound amblyopia than one with a later onset. The results in treatment of amblyopia vary directly with the age at which it is first recognized and treatment initiated. The results are 80 per cent successful when started at the age of 2 years, 60 per cent successful in the 2-4 year age group, and only 40 per cent satisfactory when started in the 4-7 year age group.[2] Beyond 7 years of age, amblyopia is very difficult to overcome, as the abnormal reflexes are more firmly established. In addition, these children so afflicted are of school age, when patching may interfere with schoolwork plus making the child's abnormality definitely apparent to others. The treatment of amblyopia ideally begins as soon as it is recognized in the preschool child. Almost all authors agree that therapy consists of constant occlusion of the better eye. For marked amblyopia, atropine and/or partial occlusion are inadequate. Children will cooperate when the parental attitude is proper. Those who are not treated correctly will develop permanent amblyopia and be potentially handicapped for industrial employment in adult life.

If the strabismus is of the alternating type, either eye is used while the opposite eye is suppressed. Since suppression alternates between the eyes, normal vision develops in each eye, but fusion is totally lacking. Glasses and atropine are of little value in this group. Usually there is no significant refractive error and often the onset is noted shortly after birth. The treatment of this type of strabismus nearly always implies surgical intervention.

The next step involves the direction of the deviation. Esotropia (inward deviation) is the most common. This can be explained on the convergence-accommodation relationship. Hyperopia is common in childhood, but those with excessive hyperopia must exert more accommodation to produce a clear retinal image. The same impulse which activates accommodation likewise produces convergence reflexes, and thus excessive accommodation is associated with excessive convergence, resulting in esotropia. Those with esotropia usually have a significant refractive error and must be examined by cycloplegic methods. Any other method is totally inadequate. Frequently this deviation responds to glasses partially or wholly. Accommodative esotropia typically is first noted between the ages of 2 and 3 years and is not excessive in amount (15° to 20° or less). Amblyopia is a common occurrence in this condition.

Exotropia (outward deviation) is infrequent under 5 years of age. It may be familial, and these youngsters rarely have significant error of refraction. If present, myopia is the usual type of error. In myopia, accommodation is not necessary for close vision and thus convergence is relaxed and divergence of the visual axis results. The visual acuity is commonly equal in the two eyes.

Vertical deviations (hypertropia) frequently may co-exist with a horizontal deviation. The vertical imbalance may disrupt fusion between the two eyes and make a latent horizontal deviation become manifest to such a degree that the vertical component is overlooked. Unless carefully searched for, the entire treatment may be unsuccessful unless the vertical component also is treated.

The fourth consideration is the search for a paretic ocular muscle. Paretic (nonconcomitant) strabismus is relatively rare in children. Unless there can be demonstrated a definite limitation of motion in one of cardinal directions of gaze, the strabismus is considered to be concomitant, which means that the muscles are capable of moving the eye in all directions, but the coordination between the two eyes is lacking.

If each of the foregoing questions is answered, the strabismus can be properly diagnosed and correct methods of treatment determined. The diagnosis—right, concomitant, accommodative esotropia—says in a concise manner that the child has a nonparalytic strabismus in which the right eye deviates inward, that the onset was around 2 years of age, that it will respond at least in part to glasses, and that the possibility of amblyopia must be carefully considered.

NONSURGICAL MANAGEMENT

As soon as the diagnosis of strabismus is established, a cycloplegic refraction must be done. (There is no satisfactory substitute.) The strength of the lenses prescribed is the maximum correction consistent with reasonable use of the eyes. Higher corrections may be necessary, but, if the glasses will not be worn, they are useless. Even low-power corrections often have an amazing influence upon reducing the angle of squint.[3] Myopic lenses may be prescribed for those with exophoria in order to stimulate convergency. Bifocal lenses have a definite place in the armamentarium of the ophthalmologist for those children whose eyes are straight with glasses for distance but who have strabismus for close work. The additional power of the bifocal lens for near vision often reduces the squint for this range and allows single binocular vision to develop. The bifocals are a temporary measure, and frequently it is necessary to stress this fact to the parents. The use of prisms in glasses is not widespread, except for small vertical deviations. Glasses should be worn for at least three to six months so that their effect may be determined before a decision is reached on other forms of therapy. The refractive status should be checked at regular intervals, because physical growth alters the requirement for lenses. Hyperopia may continually increase until the age of 7 years.

The use of "drops" has long been known in the medical treatment of accommodative esotropia. Atropine is prescribed on the basis that it paralyzes the ciliary muscle, thereby inhibiting accommodation and influencing the accommodation convergence relationship. Recently, miotics have been substituted for atropine. The rationale for their use is the production of peripheral accommodative spasm, thus eliminating the necessity for accommodative reflexes which would also stimulate convergence. In selected cases of accommodative esotropia the miotic regime has proved valuable.[1] Isoflurophate (Floropryl) ointment in 0.025 per cent concentration is used once every forty-eight hours. There are several reports of iris cysts after prolonged use, but these have subsequently disappeared after the miotic is discontinued.

Occlusion has been discussed previously.

Orthoptics is a term generally misinterpreted. It is often referred to as "exercises," which implies a muscular phenomenon. In reality, orthoptics is a mental education in the binocular skills to overcome amblyopia and improve the fusion status. The ultimate goal of all strabismus cases is a functional as well as a cosmetic result. Orthoptics, however, should be used with discretion, not indiscriminately. Since orthoptics is a learning process it requires attention, concentration, and awareness. Certain fundamental requirements for success with orthoptics are necessary: (1) a good orthoptist (!); (2) a child with at least average intelligence to cooperate (rarely under 4 to 5 years of age); (3) accessibility to an orthoptist so that the child may make office visits several times weekly for several months; (4) parental support and ability to carry out home exercises; (5) vision not less than 20/70 (6/21) in the poor eye; (6) strabismus not more than 30°, without marked limitation of the extraocular muscles; (7) absence of anisometropia (unequal refractive error).[5] The results are best in those cases of strabismus with divergence and postoperatively in monocular strabismus. Orthoptics has no value in pure alternating strabismus and in those cases with hypertropias. One must not expect the impossible from medical treatment; that is why surgical procedures have been devised.

Surgery is indicated in strabismus as soon as it is apparent that nonsurgical methods alone will not produce the desired results. Nothing can be gained by delaying, and a great deal may be lost. Scobee[4] stated that 85 per cent of patients with esotropia require surgery for a functional result. With accurate preoperative studies, the correct muscle(s) should be operated upon with the proper procedure and technique. Surgery aims at not only a cosmetic result but a functional one as well. If vertical and horizontal deviations coexist, the horizontal portion should be corrected first, unless the vertical imbalance is greater than one-half of the lateral. Even though they coexist, they should be handled separately. Surgical procedures are used to place the eyes mechanically in the primary functional position.

In children with large phorias, operation is indicated, but they must be carefully studied preoperatively in order to avoid overcorrection. Phorias tend to progress into tropias. For this reason, a phoria may need surgical correction early before binocular vision is lost.

Those vertical deviations which exceed ten prism diopters in the primary or reading positions are surgical. Weakening an elevating muscle is preferable to weakening a depressor. Any procedure which alters the ability of a muscle to move the eye into the reading position must be approached with caution, especially recession of the inferior rectus or superior oblique muscles.

The amount of surgery to be done is dependent upon the preoperative measurements, observation under general anesthesia, and actual condition of the muscles as seen at the time of operation. Large, hypertrophic muscles require less surgical manipulation than thin, atrophic muscles to produce the same effect. Anomalous insertions and adhesions will alter the procedure originally intended. There is a definite trend to divide the surgery between the two eyes rather than to perform extensive procedures on one eye which might potentially produce enophthalmos. This is especially true in alternating strabismus. In monocular squint there is no difference in the amount of correction obtained from operation on the deviating eye compared with operation on the nondeviating eye.

The time to operate in concomitant strabismus has been definitely established. So-called "early surgery" (at 3 to 6 years of age) is considered ideal. The purpose of the operation is to place the eyes in that position which permits the development of normal binocular reflexes. Unless it is performed at this age, development of these normal reflexes will not occur and the abnormal ones will become fixed. Advantages of surgery are immediate cosmetic improvement with psychological benefit, less likelihood of amblyopia, increased chance for binocular coordination, and finally, decreased length of treatment. In the past, some based their postponement of operation on the risk of general anesthesia, preferring to wait until local anesthesia could be used. With better anesthetics and qualified anesthesiologists, this objection is no longer valid. In divergent strabismus, operation can be deferred until later childhood, but the tendency toward symmetrical surgery holds for these cases also. Orthoptics plays an important role in those with divergence, but operation is frequently necessary to produce a lasting result.

Continued follow-up care postoperatively is as important as the preoperative work-up. Glasses and orthoptics are equally, if not more, important during this period. Surgical procedure places the eyes in a mechanically straight position, but only continuous expert observation will insure a functional and lasting cosmetic result. Operations are only one part of the treatment, but orthoptics does not cure incorrect surgery.

SUMMARY

The essential points in diagnosis of strabismus have been reviewed. The reasons for early diagnosis and treatment have been stressed. Current concepts in the treatment of amblyopia are elaborated, and intensive and early therapy is recommended. In nonsurgical management the use of miotics is discussed. Preoperative orthoptics and its limitations are considered. Changing concepts in the advisability of operating during the 3-6-year age group have been reviewed. Intensive postoperative follow-up is necessary to produce functional as well as cosmetically acceptable results.

CONCLUSIONS

Although strabismus management is in the realm of a competent opthalmologist, pediatricians should be aware of the current concepts and the reasoning behind them. Thus they will know the ideal time to refer children with squint to the ophthalmologist and will understand the logic of the recommended therapy.

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GENERALIZED OSTEOMYELITIS IN A NEWBORN INFANT

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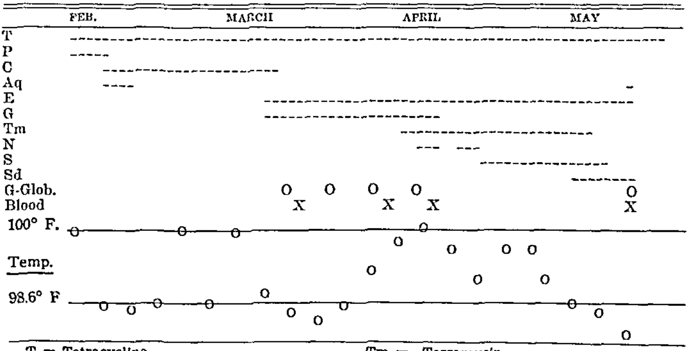
Multiple distribution of bony lesions in osteomyelitis in the newborn period being uncommon, the following case is considered of special interest.

On Jan. 29, 1956, at Gouverneur Hospital, a 5 pound 9 ounce male infant was delivered spontaneously to an Rh-positive gravida vi, para iii, 29-year-old mother. Labor was of seven and three-quarter hours' duration. The infant cried immediately and appeared to be in good condition. Routine care was given.

The mother had attended the antenatal clinic regularly, and no abnormal findings were recorded. Her past history revealed that she had had two premature infants who subsequently expired, one abortion, and her last pregnancy had been complicated by puerperal fever. Her serology was negative on two occasions.

The immediate postnatal period was unremarkable. On the fifth day, a pustular dermatitis developed around the infant's neck and inguinal regions, and then spread to the rest of the body, including the face. On the following day, his right foot became swollen and his appetite was poor. One day later, the swelling had increased and extended to the lower leg. At this time, limitation of abduction of the right leg and weakness of the foot were noticed. He had a temperature of 100.2° F., and a purulent discharge was present at the umbilicus.

Table I. Therapeutic Chart



T = Tetracycline.
P = Penicillin.
C = Chloromycetin.
Aq = Adrenocortical extract
E = Erythromycin.
G = Gantrisin.
Tm = Terramycin.
N = Neomycin.
S = Streptonivisin.
Sd = Sulfadiazine.
G-Glob. = Gamma globulin.

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Roentgenograms of both legs on the eighth day revealed extensive destruction with periosteal elevation of the proximal end of the right femur (Fig. 1). Treatment with 1.2 million units of aqueous penicillin daily and 125 mg. of tetracycline daily was instituted, and the temperature fell to normal (Table I).

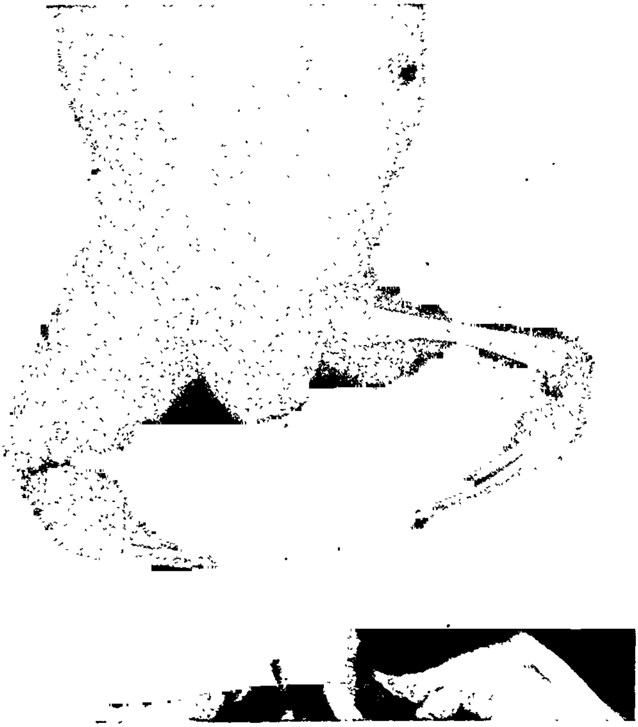

Fig. 1.

Laboratory reports at this time were as follows: Blood culture (February 5) showed *Staphylococcus aureus* highly sensitive to Terramycin, Tetracyn, Aureomycin, neomycin, and Furadantin, and resistant to both penicillin and streptomycin. Blood count (February 6) showed red blood cells, 5.6 million; hemoglobin, 17.6 Gm.; white blood cells 15,700, polymorphonuclears 71, lymphocytes 26, eosinophils 3. Repeat urinalyses were normal.

The patient then began to have frequent periods of cyanosis unrelated to feedings, which promptly responded to oxygen. On February 8 he developed oral thrush, which was almost immediately benefited by Mycostatin. His condition remained essentially unchanged until February 14, when he developed bronchiolitis with progressive respiratory difficulty, and required oxygen continuously. Rapid deterioration occurred and he appeared moribund. Chloromycetin 65 mg. orally four times a day and aqueous adrenocortical extract 5 c.c. initially and 2 c.c. every 4 hours intramuscularly were commenced. On this regimen he slowly improved and both the extract and oxygen were tapered off and then discontinued. Despite his marked clinical improvement, roentgenological findings on February 27 showed extension to the proximal right tibia (Fig. 2).

Although the infant was on Mysteclin (1 capsule daily) and Chloromycetin (250 mg. daily), he again

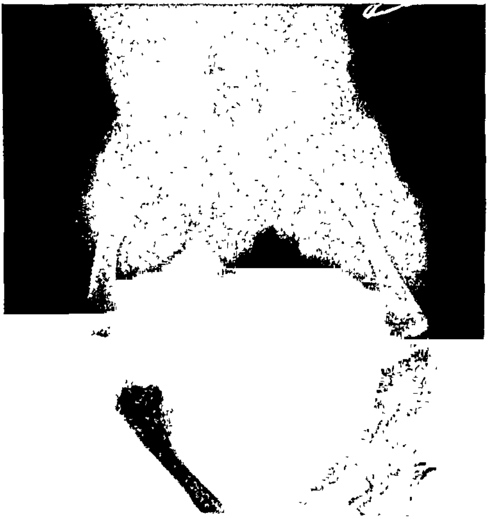

Fig. 2.

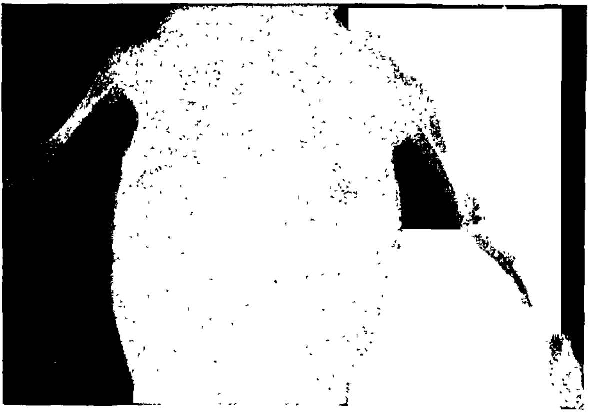

Fig. 3.

developed on March 1 a pustular dermatitis confined to the right leg and scrotum. These lesions immediately responded to Neosporin applied locally.

Laboratory reports were as follows: Culture from skin lesions (March 1) revealed *Staphylococcus aureus;* blood count (March 6) showed hemoglobin 9.5 Gm., white blood cells 31,100, polymorphonuclears 59, lymphocytes 41.

On March 14 (his forty-fourth day), his left hand became swollen and he was placed on erythromycin 125 mg. four times a day and Gantrisin 1.0 Gm. initially and 0.5 Gm. three times a day, in addition to Mysteclin and Chloromycetin which he had been on since shortly after the onset of his illness. Penicillin had been discontinued on February 24 following sensitivity studies. Swelling of the left hand persisted and on March 17 extended to the mid-forearm. X-rays on March 19 showed periosteal proliferation of the proximal ends of the radius and ulna of the right arm. The left arm, however, appeared entirely normal, apart from soft-tissue swelling.

The dosage of erythromycin was increased to 200 mg. three times a day, and the swelling of the left arm gradually subsided, with no subsequent radiological evidence of bone disease (Fig. 3). Palpable diffuse thickening of the clavicles and nodular areas involving the left posterior rib cage, without any sign of local inflammation, then appeared, and the infant's condition became worse. Three transfusions of approximately 50 c.c. each of Group O Rh-positive blood and four 1 c.c. doses of gamma globulin were administered at weekly intervals. In the course of this therapy, and while on Terramycin (30 mg. per pound of body weight), erythromycin (20 mg. per pound), and Mysteclin (tetracycline 35 mg. per pound), the infant again developed a generalized pustular dermatitis and bilateral bronchopneumonia on April 7, his sixty-eighth day. Oxygen was administered for frequent periods of cyanosis and dyspnea, and he was *given two seven-day courses of* neomycin, 100 mg. three times a day intramuscularly, with some improvement. No evidence of nephrotoxicity was demonstrated on daily urinalyses while he was on this therapy.

Laboratory reports were as follows: Blood culture (April 10) was negative. Blood count (April 17) showed hemoglobin 10.0 Gm., white blood cells 23,200, polymorphonuclears 62, lymphocytes 30, monocytes 6, eosinophils 1, basophils 1. Mantoux test 1:10,000 (April 11) was negative.

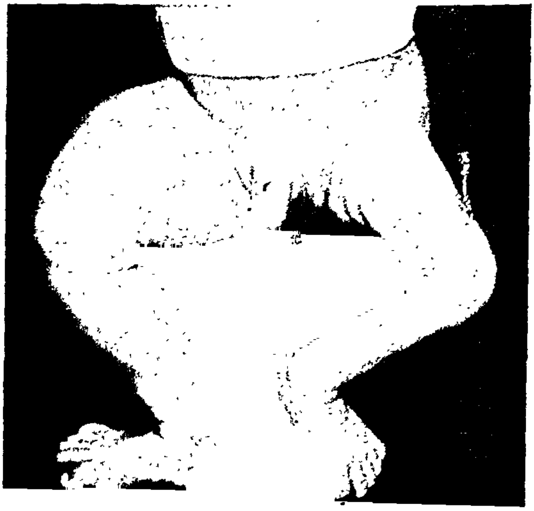

Fig. 4.

Biopsy and drainage were considered mandatory as the possibility of a sarcoma had not been ruled out. The patient was therefore transferred to University Hospital on April 24, his eighty-fifth day. On admission, both the right thigh and lower leg showed very large, extremely indurated, fusiform swellings, extending from the hip to above the knee and from below the knee to the ankle (Fig. 4). The skin, although markedly stretched, showed no signs of inflammation. The extraordinary hardness of these two masses convinced several members of the hospital staff that we were dealing with a sarcoma although there were an equal number of proponents of the diagnosis of osteomyelitis.

The patient was then given a course of Streptonivisin 62.5 mg. four times a day for two weeks, during which time muscle and bone marrow biopsies with culture were performed. These were confirmatory of chronic osteomyelitis, although cultures were negative.

His condition steadily deteriorated, and in spite of aqueous adrenal cortical extract and gamma globulin daily, he died on May 19, 1956.

Necropsy revealed large bony-hard nodular lesions of the right mid-femur and the right tibia, which presented slightly nodular smooth surfaces. On section, the cortical layers of bone were moderately thickened, measuring 2.5 cm. within the femoral and 1.5 cm. within the tibial lesion. The marrow spaces contained spicules of yellow-brown bony tissue and exuded a small amount of slightly turbid blood-tinged fluid. No gross foci of purulent material were noted in either lesion. The clavicular and costal lesions were similar. On microscopic examination, fibrosis of the marrow spaces with minimal chronic inflammatory reaction within the fibrosed areas was present in all the bony lesions. The lumbar vertebrae were not affected.

At the time of autopsy, the process appeared to be relatively quiescent, with death probably resulting from cachexia and an acute bronchopneumonia.

DISCUSSION

A number of cases of osteomyelitis in the newborn infant have been reported. To our knowledge, this is the youngest infant to be described with advanced bone destruction by the eighth day of life.

According to Blanche,[1] the incidence of osteomyelitis has decreased markedly in all age groups except in infants under 1 year. Many authorities stress the differences between osteomyelitis in infants and that in older children. The rapid periosteal proliferation, infrequency of sequestration, and rather rapid resorption when present, were thought by Green and Shannon[2] to be typical of osteomyelitis in infancy. The streptococcus was the most common etiologic factor in their series, although other studies by Green,[3] Blanche, and Thomson and Lewis[4] have found a higher incidence of staphylococcus.

In Green's report, skin infections were incriminated in 27 per cent. The incidence of skin infections in the newborn infant is common, and, as Thomson points out, their potential danger is overlooked because most of them run a benign course.

The etiology of the extensive osteomyelitis in this case was septicemia of the newborn, the portal of entry being twofold. On the fifth day he developed a generalized pustular dermatitis, and on the following day had a purulent umbilical discharge. There was therefore only an interval of three days between the known etiologic process and the positive x-ray findings. The variability between the onset of symptoms and positive roentgenographic evidence has been demonstrated by Self[5] and Ober.[6] Green found the range to be from 3 to 17 days.

Multiple bone involvement occurred in 24 per cent of Green's cases. Caffey[7] stated he had had about the same experience. He reviewed the x-rays in this case and verified the diagnosis of osteomyelitis prior to biopsy; indeed he considered biopsy an unnecessary procedure.

The diagnosis of osteomyelitis was never questioned until shortly before transfer of the infant to University Hospital. At this time, several members of the staff and other observers remarked on his poor response to therapy and the bone hardness of the swellings. Differentiation of sarcoma from osteomyelitis may be difficult. In this case, however, the patient's age, the multiple lesions, and the early course of the disease, so typical of osteomyelitis in the newborn, militated against the diagnosis of sarcoma.

Treatment necessarily had to be varied and multiple because of the many crises that had to be met during the course of the infant's illness. No agreement exists as to which treatment produces the best results. Nicholson[8] recommends immobilization in full extension and abduction. In general, most orthopedists insist upon early drainage, although the method to be utilized is still disputed. This opinion is not shared by Green, who feels that most cases respond well to early treatment with high doses of multiple antibiotics. The use of antibiotics alone in this case failed to produce the desired result.

SUMMARY

The youngest known newborn infant to have generalized osteomyelitis is presented. In spite of high doses of antibiotics instituted early, the patient died. The importance of treating skin infections in the infant is stressed. Differential diagnosis from sarcoma may be difficult.

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HAMARTOMA OF THE GALL BLADDER IN A CHILD

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PRIMARY tumors of the gall bladder are rare in children. Carcinoma of this structure is so rare under the age of 20 that our search revealed only three reported cases. Two girls were operated upon in Chile,[1] one at 17 years, and one at 14 years of age. One case was reported from Sweden[2] in a 13-year-old girl. We found no report of any type of benign tumor of the gall bladder.

Hamartomas were so named by Albrecht[3] in 1904 as "those tumor-like malformations of development in which the various tissues of a part are present in improper proportions or distributions, with prominent excess of one particular tissue." Gross[4] regards them as a development of abnormally placed tissues attempting to form substance of the parent organ, but not achieving the completely normal pattern. Potter[5] states that, except for teratomas, practically all masses present at birth and which we ordinarily describe as benign neoplasms should be included under the term "hamartoma." This includes most hemangiomas, lymphangiomas, benign pigmented moles, the neurofibromata of von Recklinghausen, adenomas of the liver, rhabdomyomas of the heart, and the cartilage-capped exostoses.

Benson and Pemberthy[6] have reported the successful removal of a hamartoma of the liver from a 7-month-old infant. Hamartomas of the lungs in children have been described, and these often showed characteristic dispersion of calcification which facilitates x-ray diagnosis. We found no reported instance of hamartoma of the gall bladder.

CASE REPORT

Michael A., a 7-year-old white boy, had been followed for three years because of a spastic quadriplegia believed due to Pelizaeus-Merzbacher's disease, a diffuse brain sclerosis associated with demyelinization of the white matter. This diagnosis[7] had been made at autopsy in two sisters who had died earlier, following a paralytic course similar to that of our patient. A maternal aunt of the patient had died of a similar condition. No special treatment for the disease is known, and none had been tried in our case. His survival this long was due almost entirely to the meticulous care provided by his mother. A brother, now 15, is apparently normal.

During an interval examination in June, 1955, an egg-sized mass was felt in the abdomen near the hepatic flexure of the colon. Over the next month this became enlarged to the size of a grapefruit. On palpation it was well circumscribed, smooth, soft, and painless. It appeared extrinsic to the liver. There had been no jaundice, melena, clay-colored stools, obstipation, diarrhea, vomiting, hematuria, or edema. Intravenous pyelograms showed normal kidney and caliceal outlines, but irregular clusters of calcium were visible in the region of the right kidney in anteroposterior views. X-rays of

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the skull and chest were negative. Blood counts and urine studies were noncontributory. Surgical consultants agreed with our impression of a malignant renal, adrenal, or retroperitoneal embryonal tumor.

Because of the incurable nature and advanced stage of the brain degeneration, it was decided that surgical exploration was unwarranted. During the next six months at home the mass continued to enlarge, finally reaching the left mid-clavicular line and the iliac crest (Fig. 1).

On Jan. 3, 1956, while the mother was holding the child, she felt the mass "break," and brought him to the office. On examination the definite mass was no longer palpable, but the abdomen was distended, diffusely tender, and there were signs of intra-abdominal fluid (Fig. 2). The acute symptoms subsided with conservative treatment, and, in April, 1,000 c.c. of very viscid, amber-colored, ascitic fluid with a specific gravity of 1.005 was obtained by abdominal paracentesis. This fluid gave a negative test for bile, a strong test for albumin, and a normal test (11 units) for amylase. A centrifuged sample, which was studied carefully by our pathologist, contained mesothelial and polymorphonuclear cells, but no tumor cells.

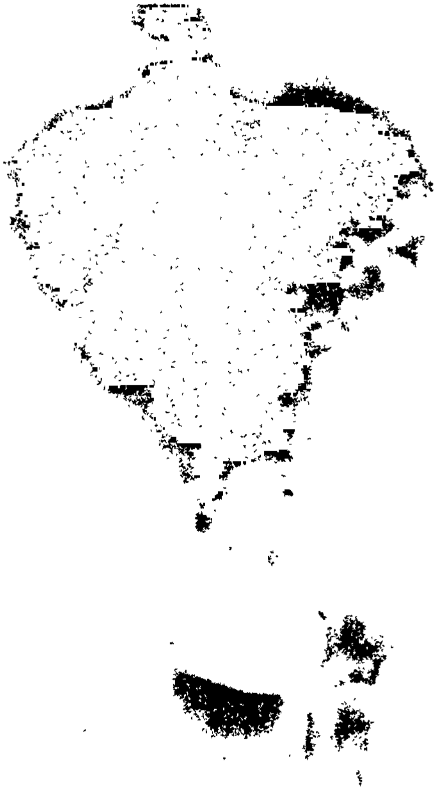

Fig. 1.

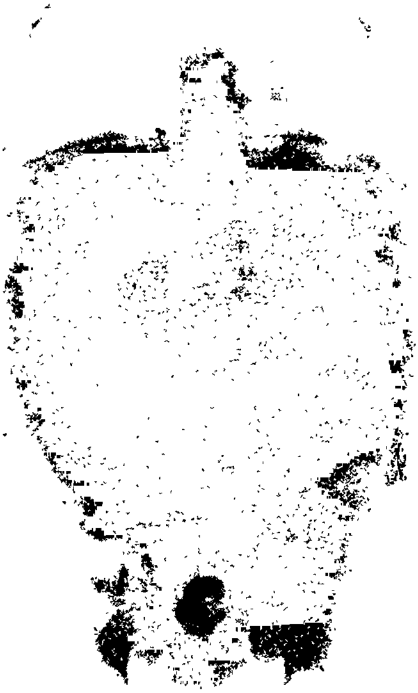

Fig. 2.

Fig. 1.—X-ray, July 14, 1955, showing lower border of tumor and normal right pyelogram.
Fig. 2.—X-ray, Jan. 4, 1956, after rupture of tumor, showing massive intra-abdominal fluid.

Since our patient had failed to show the usual downhill clinical course of malignancy, we began to doubt the original diagnosis. Review of all x-rays placed new emphasis on a lateral film showing the calcifications clustered rather more anteriorly than might have been expected for a mass originating in the kidney-adrenal area. A cholecystogram was attempted and showed no dye in the gall bladder after single and double doses of Telepaque.

Surgical exploration under ether anesthesia was performed on May 18, 1956, by Dr. R. J. Brown (following an unsuccessful attempt at splenoportogram). Five hundred cubic centimeters of amber ascitic fluid had been removed from the abdomen the day before. (Fig. 3.) More fluid escaped upon opening of the peritoneal cavity. The spleen, kidneys, and pelvic structures were normal to palpation, and no pathology was found except in the right upper quadrant. Here the omentum was strongly adherent to the fundus of the gall bladder, which was enlarged to about five times normal size. On separation of the omentum, a large defect in the gall bladder in the region of the fundus was exposed where omentum had apparently replaced the fundus wall. The gall bladder (Fig. 4) was filled with what appeared to be a mucoid type of carcinoma. There were large glands along the cystic and common ducts. The common duct was dilated. No pathology was felt in the pancreas or liver.

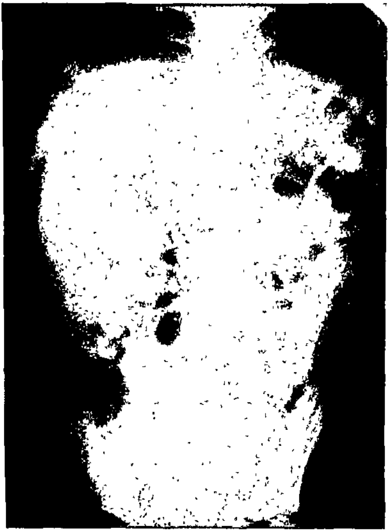

Fig. 3.—X-ray, May 17, 1956, after preoperative paracentesis, showing calcification pattern.

Cholecystectomy was performed without difficulty and the postoperative course was uncomplicated. During the subsequent eighteen months no evidence of metastasis or recurrence has been noted.

Pathology.—Dr. C. E. Black, pathologist, reported that the gross structure (Fig. 4) of the mass was cystic, with a yellow necrotic content and a thin, calcified wall. The omental segment was friable and arranged in papillary processes.

The initial impression of adenocarcinoma of the gall bladder was changed to hamartoma after review of microscopic sections (Fig. 5) at the University Hospital in Ann Arbor,[8] at the Memorial Center Children's Tumor Registry in New York,[9] and at the Children's Medical Center in Boston.[10]

Dr. Sidney Farber reported microscopic sections showing: ". . . marked proliferation of the mucosa, which is folded and reduplicated, and shows hyperplasia of the epithelium in many places. Within the connective tissue

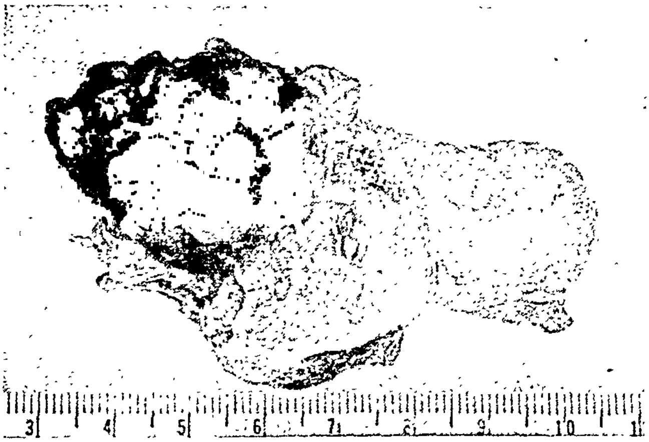

Fig. 4.—Operative specimen showing gall bladder with disruption of wall.

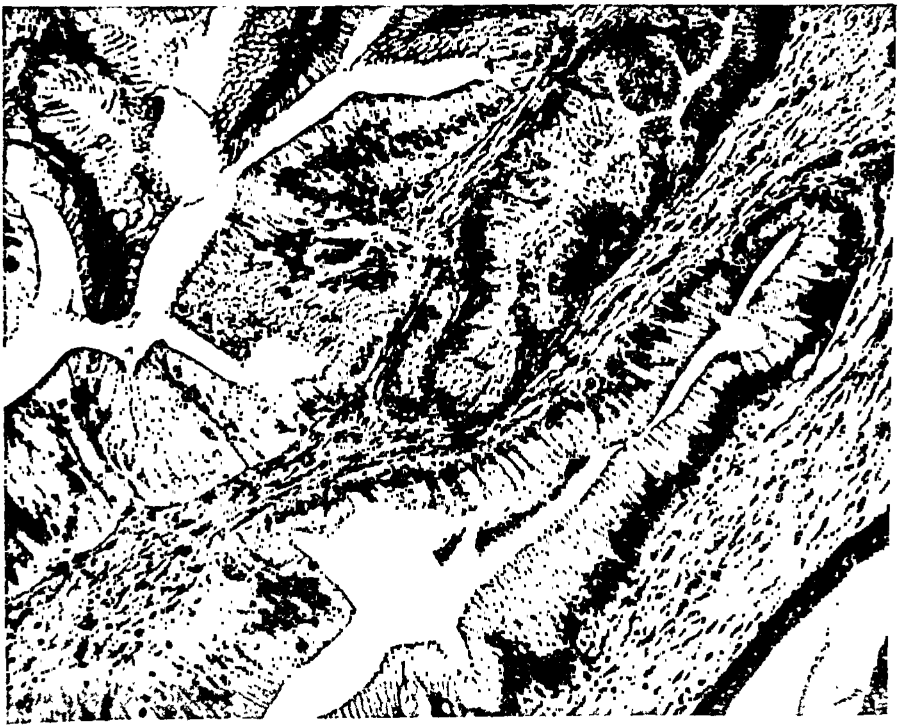

Fig. 5.—Section of hamartoma showing proliferation and hyperplasia of mucosa.

cores of the papillary projections are seen smooth muscle elements, as well as eosinophilic homogenous material. The presence of macrophages in the subepithelial tissue suggests a chronic inflammatory process. Portions of wall of a mucocele are present in association with the hyperplastic mucosa." His diagnosis was, "Hamartoplasia of gall bladder, benign, with adenomatous hyperplasia."

CONCLUSION

A case of hamartoma of the gall bladder occurring in a child is presented. The intra-abdominal occurrence of hamartoma is rare and no previous report of gall-bladder hamartoma has been found. The literature did not support a correlation between the hamartoma and the patient's coincidental brain degeneration. This tumor developed a huge mucocele, which occupied nearly two-thirds of the abdominal cavity before it ruptured. Observation for one year following successful cholecystectomy has revealed no evidence of recurrence or metastasis.

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ACUTE APPENDICITIS IN EARLY CHILDHOOD

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THE diagnosis and treatment of acute appendicitis in the very young patient present a difficult problem and place a heavy responsibility not only upon the surgeon, but also, and perhaps to an even greater extent, on the general practitioner and pediatrician. It is only when this disease is constantly kept in mind by the physician called to the bedside of the very sick infant and young child that the diagnosis can be made early and treatment instituted promptly so that the morbidity may be decreased and the mortality kept at the lowest possible level.

Snyder and Chaffin[1] stated that up to 1952 they had found 447 reports on acute appendicitis in childhood in the medical literature. This reflects the gravity of the disease and the preoccupation of the pediatric surgeon lest the standards and signs that apply to the adult patient be inadvisedly applied to the young one. The history and physical findings which are usually so typical in the adult are frequently vague, unreliable, and misleading in the young child. Also, experience has shown that acute appendicitis in the younger age group can progress with appalling rapidity to perforation.

Because of the continuing diagnostic and therapeutic difficulties that are presented by these young patients, we have reviewed our cases from 1947 through 1956. This report is based on a study of all patients under 4 years of age with acute appendicitis who were operated upon at the Babies Hospital in New York City during this ten-year period. During the same period acute appendicitis was an unexpected finding in the post-mortem examination of 5 premature infants. These cases were not included in the study.

Our series includes 83 children: 45 females and 38 males. Table I shows the distribution according to age and points out the rarity of the disease in the infant group.

TABLE I. DISTRIBUTION OF CASES ACCORDING TO AGE

AGE IN YEARS	NUMBER OF CASES	PER CENT
0 to 1	1	1.2
1 to 2	9	10.8
2 to 3	26	31.4
3 to 4	47	56.6

We found, in agreement with many others,[2-9] that the most frequent presenting symptom on admission was abdominal pain; this varied from very mild to severe, and was sometimes discovered by the mother of the patient, after other symptoms had appeared, as the only explanation for a fixed

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From the Department of Surgery, College of Physicians and Surgeons, Columbia University, and the Surgical Service of the Babies Hospital.

position of the legs in flexion or for the continuous crying of the child. We have recorded in Table II the predominant symptoms elicited by the history.

TABLE II. FREQUENCY OF PREDOMINANT SYMPTOMS

SYMPTOMS	NUMBER OF CASES	PER CENT
Abdominal pain	77	93
Abdominal pain and vomiting	64	77
Vomiting, no pain	4	5
No pain or vomiting	2	2

Interpretation of the physical findings on admission to the hospital presented a difficult task in this study. Examination of the abdomen was frequently unsatisfactory because of the lack of cooperation of the patient or the difficulty of interpretation of the physical findings. In some cases sedation was needed for the examination. In most instances the examiner made some record of the presence or absence of local abdominal tenderness and rigidity or of their subsequent development. The localization of signs to the right lower quadrant was the most frequent finding in arriving at a decision to operate. In many instances, the general picture of acute illness and a history that was compatible with appendicitis coupled with a high index of suspicion following an unsatisfactory abdominal examination led the surgeon to operate. Tenderness or the palpation of a mass on rectal examination was of particular value in this age group and in some cases it was the only significant abnormal physical finding which led to the diagnosis. The fever range was from 99° to 105° F., depending on the pathological findings and the state of hydration of the child. Leukocytosis was present in the majority of cases; 85 per cent had a white blood cell count of over 10,000; in 58 per cent the count was over 15,000. The polymorphonuclear cells were usually elevated, as expected. However, in several cases of advanced appendicitis, the white blood count was normal. In general, only minor emphasis was given to the blood count in arriving at a diagnosis in this series.

We have continued to use the pathological classification of Schullinger[10-12] in studying our cases. His more recent statistics on the distribution of the pathological types covering patients of all ages treated at the Columbia-Presbyterian Medical Center appear in Table III and are compared to the age group under consideration.[13] It is of interest to note that in a previous report from the Babies Hospital by Taylor and Hodges[14] in 1941 of

TABLE III. PATHOLOGICAL DISTRIBUTION OF CASES

GROUP	PATHOLOGICAL DIAGNOSIS	NO. OF CASES	PRESENT SERIES (UNDER 4 YEARS) (PER CENT)	SCHULLINGER[13] SERIES (ALL AGES) (PER CENT)
I	Simple acute appendicitis	9	11	68.7
II	Acute appendicitis with localized peritonitis	15	18	17.0
III	Acute appendicitis with appendiceal abscess	25	30	9.5
IV	Perforated acute appendicitis with acute diffuse peritonitis	34	41	4.6
V	Acute appendicitis with progressive fibrino-purulent peritonitis	0	0	0.2

children up to 13 years of age, the same percentage of perforated and nonperforated appendicitis cases was recorded as that given by Schullinger. The important difference is found in the younger age group being presented. This has been emphasized in a recent paper by Fields and associates,[15] who reported perforation in 31 of 38 children 3 years of age or younger.

The interval between the appearance of symptoms and the time of operation was found to play an important part in the morbidity in terms of hospital stay (Fig. 1). The delay was due to the late appearance of the patient at the hospital or to indecision of the surgeon to operate after the patient had been admitted. Some of the delay was attributed to preparation of the patient for operation (hydration, nasogastric aspiration, etc.). Whatever the cause for delay, it was evident that the morbidity was increased in nearly direct proportion to the interval.

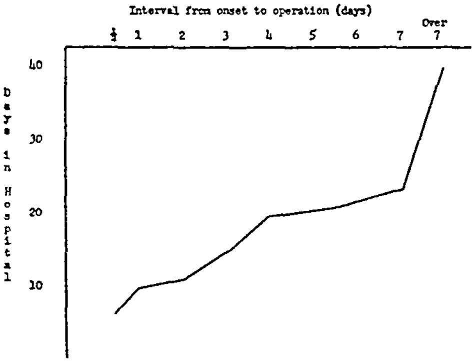

Fig. 1.—Days of hospitalization, as related to the delay between the onset of symptoms and the time of surgery.

TECHNICAL CONSIDERATIONS

The McBurney incision was used in 74 of the cases; in 11 of these a Weir extension was necessary. A transverse incision in the right lower quadrant was used in five cases, and a right rectus incision in four. The appendiceal stump was inverted in 66 of the 83 cases. In the others, the stump was doubly ligated and not inverted because of edema of the cecum or difficult exposure.

Drainage was employed in 44 of the 83 cases for the indications previously outlined by Schullinger.[12] This is a relatively high percentage of cases in which drainage was used and may attest to the return to sound surgical principles rather than to the inordinate reliance on antibacterial agents.

MORTALITY AND COMPLICATIONS

In this series of 83 cases there were 1 death and 15 complications.

The fatality occurred in a 3-year-old Puerto Rican male (U. H. 980115) who was admitted in December, 1949, having a 7-day history of abdominal pain. He was acutely ill, with signs of acute appendicitis and roentgen evidence of lobar pneumonia. Operation was done under ethyl chloride and ether anesthesia 30 hours after admission. Appendectomy, without inversion of the stump, was performed for acute appendicitis and appendiceal abscess. During the procedure there was sudden cardiac arrest. Thoracotomy was done, and cardiac massage was started 4 minutes after the arrest, with restitution of the heartbeat. Postoperatively he showed evidence of severe cerebral damage, and he died 4 months later. Diffuse cerebral atrophy was found at post-mortem examination. The operative field and the pneumonia were well healed.

The death was attributed to an anesthetic complication. One may well speculate on the outcome if the diagnosis of appendiceal abscess had been made preoperatively and operation withheld in the presence of co-existing lobar pneumonia or on the contributing roles played by the pneumonia, the preoperative delay (30 hours), and the tardy institution of cardiac massage.

The *complications* were: 8 cases of wound infection, 3 of paralytic ileus, 2 of pelvic abscess, 1 of acute gastric dilatation and 1 of thrombophlebitis. All but one of the complications occurred in cases of perforation or appendiceal abscess.

APPENDICEAL ABSCESS

As also noted by other observers, the percentage of patients who had both perforation and local abscess at the time of admission to the hospital is relatively high in this age group. In this series it was found in 25 of the 83 cases (30 per cent). The abscess was not suspected preoperatively in 11 of these cases, the diagnosis being established at operation. The small group of 14 cases in which the diagnosis of appendiceal abscess was made preoperatively was of particular interest to us since it may indicate a more recent trend in management. In 11 of these, operation was the treatment of choice (appendicectomy with drainage in 8, incision and drainage with subsequent appendicectomy in 3). In the other 3 cases conservative or nonoperative treatment was followed. These patients had "interval" appendicectomy 8 to 12 weeks later.

In the previous report from Babies Hospital in 1941 by Taylor and Hodges[14] the nonoperative treatment of appendiceal abscess was more frequently chosen and advocated.

This series is too small and the circumstances of the individual cases too variable to compare the operative and the nonoperative methods of treatment. However, it is our impression that there has been a trend toward "early operation" in these cases since the advent of the antibacterial drugs. It must be pointed out that the only death in this series was in a patient who was operated upon with an appendiceal abscess although the diagnosis was not made preoperatively.

SUMMARY AND CONCLUSIONS

1. Acute appendicitis in early childhood is a treacherous disease because the diagnosis is difficult to establish early in the illness. The frequency of perforation is inordinately high.

2. Local abdominal tenderness and rigidity or their subsequent development, and rectal tenderness or mass are the most important diagnostic signs.

3. A physical examination in this age group is too often unsatisfactory. Abdominal signs in an acutely ill, uncooperative young child may be impossible to evaluate.

4. A high index of suspicion of acute appendicitis with a history that is compatible with the disease must serve as the basis of diagnosis and the decision to operate in some cases in this age group.

5. There has been a recent trend to early surgery in cases of appendiceal abscess, in preference to conservative, nonoperative management.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

THIS 2-year-old white girl was admitted to The Children's Medical Center for the investigation of spasticity, convulsions, and mental retardation.

The child was the product of a normal full-term pregnancy and delivery. The mother was Rh negative and the father and baby Rh positive, but no rise in the mother's antibody titer was noted during pregnancy, and the baby's Coombs test was negative. The hemoglobin on the day of birth was "107 per cent."

The mother noted that the baby was jaundiced on the second and third days of life. The baby then did well, holding up her head at 3 weeks, and sitting alone at 4 months. The social responses were normal but the child was regarded as slightly lethargic, in retrospect.

At 6 months of age the legs were first noted to be stiff. At 8 months of age, creeping began, and, at 10 months, attempts to stand were made, but unsuccessfully. The child was toilet trained at 16 months and by 19 months of age was beginning to talk and was feeding herself.

When 20 months of age, the child became irritable, developed a fever of 102° F., refused to eat, and remained in bed. During this period, when poliomyelitis was prevalent in the neighborhood, her eyelids drooped, she stopped using her hands, could not get up, and had difficulty in swallowing solid foods. Because of suspected myasthenia gravis she was given Prostigmin, 7.5 mg. orally three times a day. There was good improvement after the first two doses, and then it was discontinued because of lack of further improvement. Somnolence now developed, and this was associated with generalized convulsive seizures and the development of incontinence. These continued daily for two to three weeks, then decreased to one every second or third day. No seizures had occurred in the month before admission to the hospital, though no anticonvulsants had been given. One month prior to entry she suffered a mild head injury. In the three-week period before admission, she had become more responsive, though her arms were noted to shake on attempts to perform voluntary acts.

Family History.—There is one healthy sibling 8 months of age. There is no known history of heredofamilial central nervous system disease.

The admission physical examination revealed normal vital signs. The head was 17.5 inches in circumference; the crown-heel length was 33 inches. The infant was well developed and well nourished, but nearly completely unresponsive except for a continuous twitching of the hands. There was a spastic quadriplegia with hyperactivity of all the tendon reflexes, a sustained clonus in all extremities, and a bilateral Babinski sign. Strong tonic neck patterns were elicited on both sides. The cranial nerves and the sensory examination were said to be normal. The remainder of the physical examination revealed no abnormalities.

The laboratory examination of the urine revealed no phenylpyruvic acid or other abnormalities. The blood examination gave a hemoglobin value of 11.9 Gm. per cent, an erythrocyte count of 4.96 million per cubic millimeter, a leukocyte count of 11.3 thousand per cubic millimeter, and a normal leukocyte differential on smear. The tuberculin reaction was negative. The serum nonprotein nitrogen and electrolytes were normal. Examination of the cerebrospinal fluid yielded no cells, a protein of 131 mg. per cent. No pressure was recorded. The electroencephalogram was a natural drowsing tracing with 4 to 6 per second waves as the predominant background rate, with 2½ to 3 per second high-voltage slow waves seen from the posterior leads when the patient became drowsier. There was a high-grade asymmetry in the precentral and occipital leads, the left side having a higher voltage than the right. The pneumoencephalogram was normal.

While in the hospital the child was quite irresponsive. There was some vomiting following the pneumoencephalogram; this symptom soon subsided. A repeat lumbar puncture four days after the air encephalogram revealed a reduced pressure, with 75 leukocytes, of which 10 per cent were polymorphonuclear cells and 90 per cent mononuclear cells. There were also 80 erythrocytes and a total protein of 96 mg. per cent. Gavage feeding was required for a few days after the air encephalogram. The patient was placed on cortisone (250 mg. per day) for a period of six days, and then was discharged on a maintenance dose of 150 mg. per day.

The child was followed in the Outpatient Department and displayed a progressively downhill course, with no relief of her decerebrate state. She became blind. Cortisone administration was stopped. The patient was eventually admitted to a state institution, and died there one year after discharge from the hospital, at the age of 3 years.

DISCUSSION

DR. CHARLES A. KANE.*—There are several questions which I think should be considered as one reads the protocol.

How deep was the jaundice? Was it increasing, and how long did it last? My suspicion is that it was probably physiologic rather than the deepening jaundice that one associates with kernicterus or erythroblastosis, in view of the negative Coombs test and the normal hemoglobin values.

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Except for "stiffness" of the legs with delayed locomotor development, the child then did fairly well. During the period of acute illness at 20 months of age came the first clue to some focal disturbance of neuromuscular or neurologic function. The child stopped using her hands, her eyelids drooped, she had difficulty in swallowing solid foods, and she was unable to sit. In a somnolent child who is having a fever, these symptoms would be difficult to evaluate at best. One is told that her physician suspected myasthenia gravis. I think that was a very apt observation—yet he was apparently not satisfied that it was the answer to the problem and promptly stopped Prostigmin in face of a transient improvement. I understand—although I have no personal experience with it—that occasionally pediatricians use Prostigmin to relax children with spastic conditions. Whether or not this had any bearing on her improvement at that time, I would not know.

In the short period of improvement, three weeks before entry, the child began smiling again but her arms were noted to shake when she tried to perform voluntary acts. Perhaps this was a nonspecific fatigue phenomenon in a sick child, or perhaps it did indeed represent an intention tremor which would be of great significance in view of its possible localization to the cerebellar pathway system.

On physical examination, the head diameter was about an inch smaller than it should be for a child of this age, so that a mild degree of microcephaly may be said to have been present. There was no hepatosplenomegaly noted or mentioned. This would help us to exclude such possibilities as Niemann-Pick disease and Gaucher's disease. I would assume that the fundi were within normal limits. In a child of this age, the textbook cherry-red spot of cerebromacular degeneration may not be visible, but one should see perimacular edema or some disturbance in the retinal appearance immediately adjacent to the fovea. Recently, at one of the pathological meetings it was mentioned (but I cannot find any further confirmation of this, or even *an allusion to the original report*) that in certain cases of cerebral macular degeneration one may find a high beta-lipoprotein in the blood. This is the only clue that Tay-Sachs disease may be associated with some systemic nonnervous abnormality.

I had an opportunity, just a few minutes ago, to see a small sample of the electroencephalographic tracing. It is exactly as described in the protocol, and again I would like to stress its negative aspects. I saw nothing there which resembles the triphasic wave forms which Cobb and others[1] have described in twelve cases of cerebral lipoidosis in children. These triphasic wave potentials are non-focal. They are dysynchronous, and they do not have any particular predilection for occipital or frontal areas. They are never seen in adult patients with cerebral lipoidosis. These investigators feel that if a child with diffuse encephalography shows triphasic wave potentials, one can eliminate Schilder's disease and seriously consider the possible presence of a diffuse neuronal disorder, such as a cerebral lipoidosis. Again this is negative information, and as my colleague, Dr. Joseph Foley, is prone to point out—the man who makes a positive observation is far ahead of the man who makes a negative observation.

The pneumoencephalogram was negative, which helps me to exclude subdural hematoma and a large infiltrative tumor or abscess near the ventricles.

A brain biopsy would have been of some interest in this child. Recently, at the Boston City Hospital, we had the neurosurgeons do a brain biopsy in a similar case where prognosis was of great importance since the child had two younger siblings. In such a biopsy one can usually exclude or establish diffuse neuronal disorders such as lipoidosis. In our particular case we were disappointed to have a nonspecific report. It has also been pointed out that if these children with diffuse neuronal lipoid disorders have to undergo an abdominal operative procedure, or if a biopsy of an autonomic ganglion such as the stellate is performed, the pathologist may find the typical swollen neuronal cells.

The only thing that we should perhaps discuss further is what interpretation we should give to the second spinal puncture done four days after the pneumoencephalogram. The introduction of air in the spinal subarachnoid space is a moderately irritating procedure, even in children, and my interpretation of the second spinal fluid finding is that they would not be inconsistent with a sterile meningeal inflammatory reaction due to the introduction of air. I do not believe they represent a primary or chronic meningeal inflammatory disease.

Now, I believe that there is one key word in this protocol. This is "twitching," and I would like to find out as much as I can about this. Was it actually myoclonic with rapid jerk-like movements of the extremities, or was it a fine rapid tremor?

Dr. Peter Auld.—The record states: "There is a continued twitching of the hands when the child is placed on her abdomen, and there are gross clonic movements."

Dr. Kane.—Was this myoclonus or myoclonic epilepsy? Myoclonic epilepsy refers to a familial syndrome described originally by Unverricht[2] and more recently by Lundborg[3] with progressive dementia, spasticity, quadriplegia in flexion, and a peculiar type of epilepsy which is remarkably sensitive to audio, visual, and proprioceptive stimuli. If you clap your hands beside the ear of one of these children, he will have a quick, lightninglike flexion contraction of one or many of the muscles of his body. This syndrome has been described since in a variety of forms. Recently, Dr. Denny-Brown and Dr. Wesley Watson[4] at The Boston City Hospital have been investigating its pathology and electrophysiology. Physiologic myoclonus may occur in normal people on waking with a start, but when it progresses to various parts of the body and is associated with dementia, incontinence, and speech disturbances, the syndrome of Unverricht or Lundborg or, at least, some sort of diffuse neuronal disorder must be considered.

Did the twitching in this child actually represent myoclonus or not? If it did, I can make one of four quite specific diagnoses. If it did not, I have to arrive at some other conclusion. What are the four possibilities, on the basis of myoclonus as a symptom of a diffuse neuronal disease?

Any child who is jaundiced at birth certainly has to be considered as a possible candidate for the late complications of kernicterus. I would use the following evidence: (1) The child was not deaf. (Dr. Byers and Dr. Crothers at this hospital have recently reported that in a large series of cases of kernicterus there is a remarkable degree of perceptive deafness. Only one out of twenty-three children in their group failed to have a perceptive deafness.) If this child did not hear well, the odds are against this illness being a late complication of kernicterus. (2) Convulsions are rare in kernicterus. (3) This was a first-born child. (4) The laboratory data are not suggestive of kernicterus—to eliminate that possibility. Yet, I would not be shocked if some damage to the dentate, olivary, or hypothalamic nuclei were found at post-mortem. Therefore, we would have to list kernicterus as a possibility, although I am eliminating it for the moment. Now, as far as the second possibility is concerned, very briefly, the neuronal disorders that we must consider here are those which are lumped under the term "cerebromacular degeneration" and by definition this does not mean just Tay-Sachs disease, but what Dr. J. Godwin Greenfield, the dean of neuropathologists in England and on the Continent prefers to call "Batten's disease," because Batten actually described these before Spielmeyer, Vogt, Bielschowsky, or Kufs. These appear to present a spectrum with very severe cases early in life and mild cases later in life. There is a possibility, then, that this might be a form of diffuse cerebral lipoidosis, though we can, I believe, eliminate the systemic lipoid disturbances, such as Gaucher's, Niemann-Pick's, or Hurler's.

The third possibility is so-called "myoclonus epilepsy with inclusion bodies." A fourth possibility is Dawson's encephalitis, or so-called "subacute inclusion body encephalitis." Such cases have been described by Greenfield.[5] These patients with so-called (subacute) inclusion body encephalitis live from a few weeks up to 2 years, and as far as I can tell from reading the protocols, may manifest exactly the same clinical symptomatology as the patient under discussion. Both are rare and almost never correctly diagnosed in life.

If this is *not* true "myoclonic epilepsy," this brings us to the diffuse scleroses, such as Schilder's disease, or the Pelizaeus-Merzbacher syndrome, a more chronic form of the same process. Greenfield,[6] again, has introduced a confusing element into the situation and has described another form which he calls "late infantile metachromatic leuko-encephalopathy," which resembles in some ways the diffuse scleroses, and yet appears to be atypical.

I have been trying to determine what there is about the case that led to the introduction of cortisone therapy. Cortisone has been used by neurologists for a variety of different reasons—among them the treatment of neurological complications of certain collagen diseases. It has a limited use in tuberculous meningitis, with which I am sure you are familiar, and one or two enthusiastic groups of workers have attempted to use it in myasthenia gravis. I am sure it has no place in the latter situation. The dose used here seems to me to be rather large for a child weighing 40 pounds, in terms of the dose one would use in an adult.

If I were to make a guess—and I think there is no point in discussing a protocol unless you do make a guess—mine will be predicated on the belief that these were true myoclonic twitchings, and, therefore, my conclusion is that this is probably not diffuse gray matter disease, such as Alpers disease, nor one of the diffuse scleroses, but one of the types of diffuse neuronal disorders which we mentioned—a cerebral lipoidosis, myoclonic epilepsy, or one of the inclusion body encephalitides. My final statement is this—if this is true, then the spinal fluid is distinctly unusual. The spinal fluid would fit in better with Schilder's or one of the demyelinating types of diffuse sclerosis than it would with one of the cerebral lipoidoses. So, I am on the horns of the traditional dilemma. Either I believe the spinal fluid and diagnose Schilder's disease or something akin to it, or else I do not believe the spinal fluid, interpret the twitchings as myoclonus epilepsy, and diagnose diffuse neuronal disorder.

Dr. Farber.—Do you have any ground for disbelieving the spinal fluid?

Dr. Kane.—No, I do not. I accept that. It just poses a problem in the sense that in the diffuse neuronal disorders, one would *not* expect the spinal fluid to show an elevated protein, whereas in Schilder's disease it is possible. I am quite sure about one thing. I doubt that this child had myasthenia gravis.

Dr. Farber.—I think the dilemma is one which has perplexed us many times. Should we accept a laboratory finding which appears to be clean-cut, but which is not entirely consistent with the clinical picture, or shall we stress the clinical findings and disregard the laboratory evidence which is not consistent with the clinical picture? Perhaps this discussion will bring out the feelings of the house staff. Dr. Berenberg, may we begin with you? Is this myasthenia gravis?

Dr. William Berenberg.—I would agree with Dr. Kane that this is not myasthenia gravis. Is this not perhaps an individual who has had spastic quadriplegia of cerebral palsy, who then went on to a convulsive state, as so many of them do? I agree with your statement about the rarity of convulsions in those who have had kernicterus, but certainly such terminal states are common enough in those who have gone on to a diffuse degeneration as a result of repeated seizures. I was more impressed with the spinal fluid values than you were, Dr. Kane, particularly because two readings were significantly elevated. I would be inclined to put the case in a degenerative group for that reason alone. I would like to ask Dr. Kane if the pneumoencephalogram helps at all in differentiating these degenerative states?

Dr. Kane.—Not particularly, Dr. Berenberg, except in a sense that if the process resulted in hydrocephalus, we would expect an abnormal pneumoencephalogram. I think it is quite conceivable that a child might have any one of the syndromes that we mentioned with a perfectly normal pneumoencephalogram.

DR. MARTIN H. WITTENBORG.—I am not prepared to say that the pneumoencephalogram of this patient is quite normal. The cranial vault is borderline in size and at the lower limits of normal size. By itself, I think that would mean very little. The lateral ventricles are top normal in size, again a finding, in itself, of doubtful significance. With a head which is smaller than normal and with the ventricles a little larger than normal, you can say that some diffuse diminution in the total mass may be present, provided there is no obstruction of any sort.

DR. KANE.—This would, perhaps, be against Schilder's disease.

DR. WITTENBORG.—I think so. I think that we see this sort of thing in older age groups in many conditions. I have no idea whether this represents hypoplasia or diffuse decrease in brain substance.

DR. CRAIG.—Would not your encephalogram be of more diagnostic value later in the course of the degenerative process and show some atrophy in these children?

DR. KANE.—The clinician may get a clue as to the presence of Schilder's disease in that, of all the degenerative encephalopathies, it is the one which may be associated with papilledema, an increased intracranial pressure, and an elevated spinal fluid protein. During the preliminary phases of degeneration, the myelin becomes swollen and this produces a papilledema, or at least a swelling of the optic disk.

DR. FARBER.—The swelling may be so great in Schilder's that on one occasion, twenty-five years ago, a clinical diagnosis of bilateral glioma of the optic nerves was made. At post-mortem, indeed, these optic nerves were huge. The late Dr. Myrtelle M. Canavan,[7] who studied that brain with the well preserved optic nerve swelling, found a typical example of Schilder's microscopically.

DR. RICHMOND S. PAINE.—We who followed this child believed that she had one of the degenerative diseases of the white matter of the Schilder's group. We felt that a differential diagnosis between the different members of the group could not be made during life. The protocol does not fully indicate the progressive nature of the child's illness.

There have been various word-of-mouth reports that Schilder's disease and others of that group are supposed to be benefited by cortisone. There are two such cases which Dr. Sydney Gellis is following at the Beth Israel, one of which had, on pneumoencephalography, what appeared to be a mass projecting into one lateral ventricle. At operation, this mass was found not to be a tumor, but rather a mass of degenerating myelin of the Schilder type and it was felt, therefore, that the diagnosis was confirmed. That child improved very dramatically on cortisone. I have seen her several times since, on and off cortisone. Each time she was better on the cortisone and worse without it. The other patient has, I strongly suspect, multiple sclerosis rather than Schilder's disease and is naturally having her ups and downs. Because of the possibility that cortisone might be of benefit, it was tried here, with no great success as the ultimate outcome obviously showed.

DR. KANE.—It would have been of great interest in this case to do a quantitative test for gamma globulin by the zinc sulfate precipitation test developed by Dr. Joseph Foley at the Boston City Hospital, after eliminating liver disease and neurosyphilis. This test is now somewhere between 85 and 90 per cent accurate in making a very strongly suggestive diagnosis of a demyelinating disease. The levels of gamma globulin that he would consider significant are somewhere on the order of 15 per cent of the total protein, or more. If the percentage of gamma globulin in the spinal fluid exceeds 15 per cent of the total in a patient with various neurologic symptoms, the presumption is that they may well be due to multiple sclerosis. I do not know whether any such tests have been tried in patients with Schilder's disease.

DR. CRAIG.—In this child, the immediate cause of death was a very extensive hemorrhagic bronchopneumonia, in which numerous coccal bacterial forms were easily demonstrable. The brain had quite classical changes of Schilder's disease. It was 300 Gm. below the standard for the child's age. The ventricles were mildly dilated, and this appeared to be due to loss of brain substance, since no obstruction was demonstrable. There was a marked decrease, grossly, in the differentiation of the gray and white matter (Fig. 1) and many small cystic spaces were present in the depths of the white matter. Large brain sections, prepared by

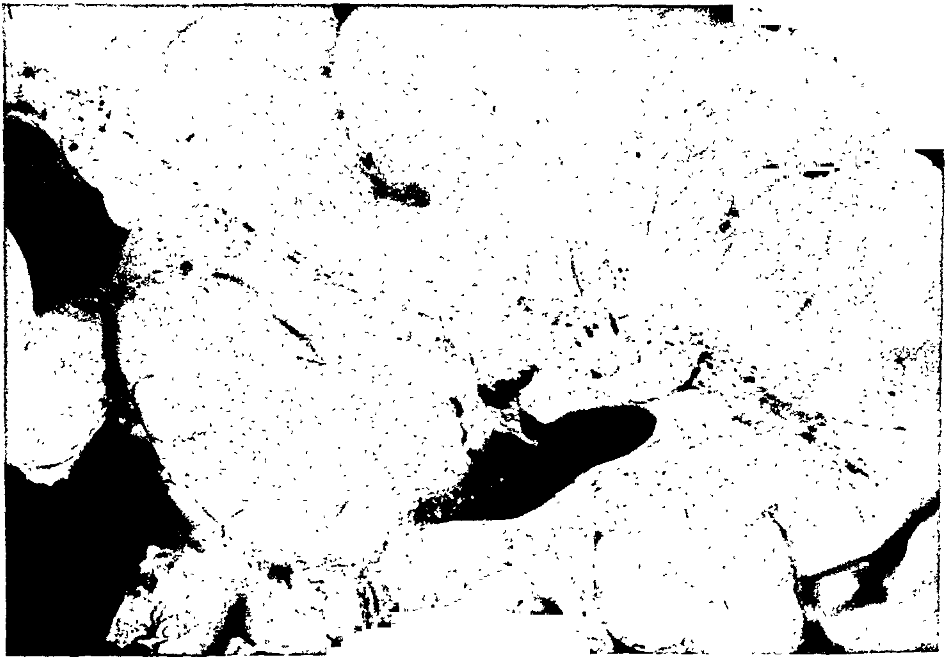
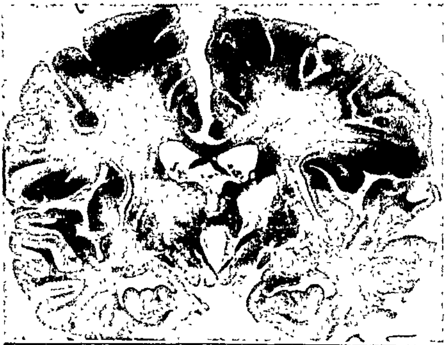


Fig 1.—Cross section of the brain. The white matter is translucent and depressed. There is little demarcation between gray and white matter.

Dr. Paul I. Yakovlev of the Harvard Medical School, revealed a very marked loss of myelin in many areas of the brain, especially in the centrum ovale (Fig. 2). As is usual in Schilder's disease (encephalitis periaxialis diffusa) the arcuate fibers running from one gyrus to an adjacent one were preserved. A Sudan black fat stain (Fig. 3) of the white matter shows few myelin sheath structures and many fat-filled macrophages to be present, both diffusely and in a perivascular distribution. Though the cerebral neuronal stripe was well preserved, there was considerable loss

Fig. 2.



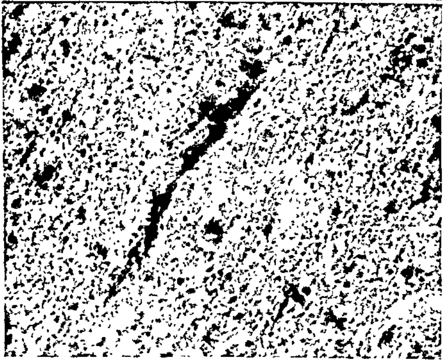


Fig. 3.

Fig 2.—Photograph of brain section. There is marked demyelination of the white matter, especially the centrum ovale and internal capsule. The arcuate fibers are partially spared. Loyez stain. (Reduced from normal size by 9/11.)

Fig 3.—Photomicrograph of brain An area from the subcortical white matter with marked demyelinization and irregular masses of lipid having some perivascular accumulations. Frozen section; Sudan black stain. (×330.)

of neuronal elements from the dentate nucleus in the cerebellum, the inferior olivary nuclei in the medulla, and in the spinal cord. These latter changes are considered to be secondary, perhaps to the anoxic spells associated with her convulsions. The other cerebral degenerative states of childhood such as the concentric form of Barlow, that of Pelizaeus and Merzbacher, the metachromatic leukoencephalopathies, and Krabbe's disease can, I believe, all be eliminated on an anatomic basis of distribution and the type of tissue reaction.

Many different etiologic considerations have been evoked in the attempt to explain Schilder's encephalitis, including allergic, infectious, viral, hereditary, and metabolic mechanisms. None have been incriminated without doubt.

DR. KANE.—The predominant opinion among neurologists and neuropathologists is that these demyelinating diseases represent a spectrum of the hypersensitive reaction in the nervous system, from slowly progressing lesions (as in some cases of multiple sclerosis) to very rapidly progressing processes (as in the so-called hemorrhagic leukoencephalopathies). It is of interest that the gamma globulin of the cerebrospinal fluid may be elevated in some of these states, which is, of course, of interest in view of the relation of gamma globulin to the immune states.

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Medical Progress

THE TONSIL-ADENOIDECTOMY ENIGMA

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> "From inability to let well alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, science before art, cleverness before common sense, from treating patients as cases, from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us."
>
> *Sir Robert Hutchison*
> (Brit. M. J. 1: 671, 1953)

No operation in childhood is performed as frequently as T and A. Contrary to the view of many discriminating physicians, the procedure is as popular now as it was 20 years ago, perhaps more so. Yet evidence of its beneficial effect is of the most tenuous sort. The operation retains its vogue in the face of well-documented evidence that, in the overwhelming majority of cases, it is useless.

T and A is generally regarded as a harmless procedure. It was so regarded 20 years ago. In the light of the clearly demonstrated relation between T and A and bulbar poliomyelitis, we now know that it was in no sense a procedure to be taken lightly. Over the years many children have died, many others have lingered in respirators, clinging desperately to an existence which offered at best permanent crippling, because of a T and A decided upon casually.

Newspapers and health insurance publicity have helped to keep alive the popularity of the operation. In an article in the staid *Wall Street Journal* (Nov. 2, 1955) under the headline—"Boonton, N. J., Group Cuts 'Frills,'" we find the following: "At 9 o'clock this morning, 65-bed Riverside Hospital here will open its doors for the first time. Exactly one hour later seven year old Diane Pierce is scheduled to have her tonsils taken out."

The *New York Times* (Dec. 25, 1956), writing about the blessings of the new "medicare" program, says, "A heavy backlog of tonsil cases involving sons and daughters of servicemen is being whittled down by civilian physicians."

Blue Shield (April 2, 1952) boasts: "A few months ago five branches of the Giordano family received $300 worth of benefits within a few days as the need for surgery swept the children. Eleven of 33 grandchildren of Paul Giordano required tonsillectomies."

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THE FREQUENCY OF T AND A

Data on the frequency with which tonsils are removed are difficult to obtain because there is no uniformity in the practice in different communities. The report of the Chief Medical Officer of the Ministry of Education for England and Wales for the years 1952 and 1953[1] points to the puzzling variations in the T and A rates in different areas. Some of these are shown in Table I. In Leeds, for example, the chances of a child having had a tonsillectomy in 1953 were 10 times greater than in nearby Sheffield.

Table I. The Percentage of School Children Operated Upon for Tonsillectomy in Various Cities in England, 1953*

	SCHOOL POPULATION	PER CENT OF SCHOOL POPULATION OPERATED UPON
Leeds	70,988	4.2
Sheffield	76,811	0.42
East Ham	16,868	3.2
West Ham	28,279	0.46
Manchester	108,080	1.7
Liverpool	131,275	0.36

*Source: The Health of the School Child. Report of the Chief Medical Officer of the Ministry of Education for the Years 1952 and 1953. P. 21, 1954.

Even more striking are the 1954 figures supplied by the Registrar General.[2] A child in Rutlandshire is 19 times as likely to have a T and A as one in neighboring Cambridgeshire; and in sunny Bexhill the operative rate is 27 times as great as in northerly Birkenhead.

A similar situation exists in the United States. Schlesinger's[3] data show that the proportion of children, 3-9 years, who had T and A's was 3 times higher in Newburgh, N. Y., than in adjacent Kingston; and, in a survey of the practice of T and A among physicians specially interested in children, Wolman[4] found that a relative small proportion of physicians are doing a disproportionately large number of operations.

A further difficulty in estimating the frequency of T and A is that the socioeconomic grouping is an important consideration. In the study made by Downes[5] in Westchester County, N. Y., children of the professional and managerial class were much more likely to be operated on than those of the semiskilled and unskilled group.

In England, Glover[6] found that T and A was performed more than 3 times as often in children of the well-to-do as in those who attended public elementary school. At Eton, in 1938, 83 per cent of new boys had had their tonsils removed before entry at about 13 years of age. In general, the wealthier and more exclusive the school the higher the tonsillectomy rate.

A study of T and A in Australia has been reported by Dey.[7] He surveyed a group of approximately 700 children who had been recommended for T and A by experienced members of the visiting staff of the Sydenham Children's Hospital but who were not operated on because of a poliomyelitis epidemic. On re-examination 18 months or more later it was concluded that operation was unnecessary in 37 per cent. Dey also found that 49 per cent of a series of children attending free public schools in Sydney had had T and A's, while more than 70 per cent of children attending private schools had lost theirs.

In 1932-33, the American Child Health Association[8] presented data on the frequency of T and A in 1,000 children from the public schools in New York City. At that time 61 per cent of the children had had their tonsils removed by the time they were 11 years of age.

Seventeen years later, Siegel, Greenberg and Magee[9] surveyed the situation again and discovered that 53,007 T and A's had been performed in the hospitals of New York City during 1949. The average annual number of births during the 5-year period, 1940-1944, was 117,344. Using this figure as a measure of the child population, and assuming that 1949 was a representative year for T and A, then roughly 45 per cent of New York City children had had their tonsils removed in hospitals in the city. Surprisingly, however, a considerable number of New York children are operated on in the private offices of physicians and outside the city. Of 74 children with poliomyelitis, Siegel, Greenberg, and Magee found that 24—almost a third—had had tonsillectomies elsewhere than in New York City hospitals. It is hardly justifiable to generalize on the basis of this small sample but evidently a 45 per cent estimate of children operated in New York City is low. The frequency of T and A was probably not materially different in 1949 from what it had been in 1932-1933.

Downes,[5] working in 2 communities in Westchester County, N. Y., found that T and A has risen sharply during the past 5 decades. Of persons born before 1910, 19 per cent had been operated on by the time they reached their twentieth birthday. Among those born between 1910 and 1929, 48 per cent had lost their tonsils by the same age; and of those born after 1929 the figures had risen further, to over 55 per cent. In families where the head was of the professional or managerial class the percentage of T and A's in the youngest group (born after 1929) was 67.

Another interesting feature brought out by Downes' report is the earlier age at which T and A is now performed. For example, in males 40 years and over in 1949, only 4 per cent had lost their tonsils by the time they were 5 years old, compared with 18 per cent in the 20- to 39-year-old group and 42 per cent in the under-19-year-old group.

TABLE II. COMPARISON OF THE FREQUENCY OF TONSIL-ADENOIDECTOMY IN 1943 AND 1951, ROCHESTER, N. Y.*

AGE—YEARS	PER CENT OPERATED UPON	
	1943†	1951‡
14	51	61
15	51	59
16	58	57
17	50	55
14-17	52.5	57.5

*Source: Dr. Albert D Kaiser.

†Based on 40,454 examinations in all schools.

‡Based on 821 minors examined for work permits.

The late Dr. Albert D. Kaiser (loc. cit.) supplied data on the frequency of T and A in Rochester, N. Y., in 1943 and 1951 (Table II). The number of operations increased from 52.5 per cent of teenagers in 1943 to 57.5 in 1951.

According to the Registrar General's report for 1954,[2] 226,211 T and A's were done in National Health Service Hospitals. This does not include patients operated on in private hospitals and nursing homes. Since the number of births in England and Wales is about 670,000 a year, this means that one third or more of British children are having T and A's.

The tonsillectomy fad is world-wide. Even in faraway India, Wagle[10] deplores the frequency of the operation.

The Metropolitan Life Insurance Company has recently published figures on the frequency of admissions to hospitals of the dependent children of the company personnel (Table III). T and A's accounted for nearly half of the operations in children under 20 years; the proportion under 10 years exceeded two thirds.

TABLE III. THE ANNUAL HOSPITAL ADMISSIONS PER 1,000 DEPENDENTS OF PERSONNEL, METROPOLITAN LIFE INSURANCE COMPANY, 1954-55*

	ALL TYPES OF SURGERY		TONSILS AND ADENOIDS	
AGE (YEARS)	MALES	FEMALES	MALES	FEMALES
0-19	46.2	38.8	21.9	20.7
0-4	38.7	25.0	17.4	13.6
5-9	69.3	62.5	47.5	43.7
10-14	33.3	28.7	7.4	11.3
15-19	36.1	35.6	4.1	4.6

*Source: Statistical Bulletin, Metropolitan Life Insurance Company, April, 1957.

According to data obtained from the Michigan Medical Service (M M S), this plan paid for about 44,000 T and A's in 1955 (12 operations per 1,000 members). If the frequency of operations was the same for persons not insured by the M M S, then about 88,000 T and A's were performed in Michigan in 1955. Since the annual number of births for the past 10 years has averaged about 160,000, this means that over half the children in Michigan are having tonsillectomies.

Le Riche and Stiver[11] report that the annual rate for T and A in 1955 was 19.8 per 1,000 members insured in the Physician's Services, Inc., Ontario. The frequency by age corresponds closely with the Metropolitan Life Insurance Company data.

WHY ARE TONSILS REMOVED?

An interesting approach to the T and A problem was that of Wolman[4] who surveyed, by questionnaire, 3,441 physicians with practices confined principally to the care of children. Among the questions asked was, "What do you consider indications for tonsillectomy and adenoidectomy?" The replies are summarized in Table IV.

Thirteen indications are given. Heading the list is "recurrent or chronic otitis media," which was included in every physician's reply. Other indications prominently mentioned are mouth breathing or snoring due to large size of tonsils or adenoids, recurrent or chronic tonsillitis, early hearing impairment, recurrent or chronic cervical adenitis, peritonsillar abscess, recurrent or chronic asthma induced by respiratory infections, "tendency" toward rheumatic fever, recurrent or chronic sinus infection, and recurrent or chronic lung infection.

Others[12, 13] have listed more "indications" such as suppurative sinusitis, general underdevelopment associated with frequent attacks of adenotonsillitis or excessive adenotonsillar hypertrophy, speech defects associated with excessive adenoid and tonsil hypertrophy, foul breath, diphtheria carrier state, snoring, high-arched palate, pigeon breast, pyelitis, retarded mental development due to anoxemia, nightmares, night sweats, cough, and enuresis.

In actual practice, the overwhelming majority of children are operated upon for one or more of three reasons: parental pressure for the operation, large tonsils or adenoids, and frequent upper respiratory infections.

TABLE IV. THE INDICATION FOR TONSILLECTOMY AND ADENOIDECTOMY*

INDICATIONS	SIMULTANEOUS TONSILLECTOMY AND ADENOIDECTOMY (PER CENT)	TONSILLECTOMY ALONE (PER CENT)	ADENOIDECTOMY ALONE (PER CENT)	TOTAL† (PER CENT)
Recurrent or chronic otitis media	77.2	0.9	21.9	100.0
P[illegible]	66.9	1.2	19.8	87.9
R[illegible]	80.1	5.7	0.7	86.5
Early hearing impairment	58.4	0.9	26.9	86.2
Recurrent or chronic cervical adenitis	55.4	3.7	0.8	59.9
Previous quinsy (peritonsillar abscess)	47.5	9.1	0.7	57.3
Recurrent or chronic asthma induced by respiratory infections	35.5	0.3	1.7	37.5
"Tendency" toward rheumatic fever	32.8	1.2	0.4	34.4
Recurrent or chronic sinusitis	24.5	0.6	5.9	31.0
Recurrent or chronic lung infection	23.0	0.5	1.2	24.7
Scarred or cryptic tonsils	7.6	1.8	0.1	9.5
Large size alone	6.2	1.7	1.3	9.2
Routine	0.5	0.1	---	0.6
Others	2.7	0.4	1.0	4.1
No answer (0.6 per cent)				

*Source: Wolman, I.,[4] with the kind permission of the author.

†This "Total" column portrays the relative importance ascribed by pediatricians to the indications listed.

Despite much propaganda against indiscriminate tonsillectomy in the past 20 years, parents continue to press strongly for the operation. There is still a widespread impression among the laity that it is, in some way, a desirable health measure and that it protects against colds. Health insurance plans have fostered the operation. Now that it is "free," the physician, in considering the need for T and A, is no longer deterred by concern about the cost to the patient and consequently judgments are made with less deliberation.

In this connection, an interesting observation was made by the American Child Health Study Group.[8] They found that 28 out of 29 of the children, taken to a free clinic with their school medical examination slips calling attention to their tonsils, were operated on whereas none of the 7 children who went to private physicians were operated upon.

Size of Tonsils and Adenoids.—The use by physicians of tonsillar size as an indication for operation was investigated by the American Child Health Association in 1932-1933.[8] The tonsil problem was part of a larger survey of the effectiveness of school health services. Whereas in the case of most defects—dental, visual, auditory—their study was directed toward finding better ways of correcting defects which were discovered, in the case of tonsils the inquiry took a different course, namely, toward explaining the large number of tonsillectomies.

A sampling of 1,000 children, 11 years of age, from the public schools of New York City disclosed that 61 per cent had already lost their tonsils. The remaining 39 per cent were examined by a group of school physicians who selected 45 per cent of these for T and A and rejected the rest. The rejected children were then reexamined by another group of physicians, who recommended for operation 46 *per cent of those* remaining after the first examination. When the rejected children were re-examined a third time, a similar percentage—44—was selected for operation, so that after 3 examinations only 65 children out of 1,000 remained who had not been recommended for T and A. These subjects were not further examined because the supply of examining physicians had run out.

The study showed that there was no correlation whatsoever between the estimates of one physician and that of another regarding the advisability of operation. The authors therefore concluded that the chance of a child's being recommended for operation depended principally on the physician rather than on the child's health status.

The American Child Health Association study revealed that nurses were giving much more attention and time to the medical examiner's tonsil recommendation than to other health defects. In a sample of 382 11-year-old children with extreme dental defect, 53 per cent had had their tonsils removed and, in a group of 342 children with uncorrected visual defect, 46 per cent had had tonsillectomy. Here were 2 groups of children, with extreme handicaps for which nothing had been done, yet they had had tonsillectomy.

A study, not often enough discussed in the voluminous literature on T and A, is by Epstein[14] from the clinic of the late Dr. Joseph Brennemann. He followed 540 children, ranging in age from 2 to 13 years, before and at intervals for 2 years after operation.

He observed no relation between the size of the tonsils and the results of the operation. Nor could he detect any connection between the size of the crypts and the amount of caseous matter which they contained, on the one hand, and the results of the operation, on the other. Buried tonsils were no different from others in the type or severity of preoperative symptoms, in the rapidity of recovery from the operation, or in the final results.

In 152 of the children, histologic sections of the tonsils were studied. Practically all showed some degree of infection or connective tissue scars or both. There was no correlation between the histologic appearance of the tonsils, the type or severity of the preoperative symptoms, or the result of the operation. "Whether the tonsils were buried, cryptic, smooth, large or small, bore no relation to the preoperative symptoms or to the degree of success of the operation." For example, some healthy-looking children with no complaint except mouth breathing had tonsils which were riddled with abscesses and sealed off with scar tissue. Conversely, other children with an almost constant complaint of sore throat accompanied by severe systemic reactions, had almost normal tonsils.

No correlation was found between the size of the adenoids, determined by digital examination under anesthesia, and the results of operation. Although all the children with almost completely obstructed nasopharynges suffered from some degree of mouth breathing, a surprising finding was the sizable number of children with only slight narrowing of the nasopharynx who were also mouth breathers. Of 37 children with practically no obstruction in the retropharyngeal space, 20 showed some degree of mouth breathing and 11 were almost constant mouth breathers.

Even more surprising was the fact that these children were frequently cured of mouth breathing by the operation. Six of the 11 children who had little nasopharyngeal narrowing on digital examination and whose adenoids on removal were small but who were constant mouth breathers were completely cured and 2 others were improved by operation.

Epstein concludes that the appearance of the tonsils should never influence one's judgment as to the wisdom of removing them to improve the child's health. "The physician does not know an infected tonsil when he sees one."

Respiratory Infections.—Probably the most common reason why tonsils are removed, regardless of the indications listed by physicians, is to prevent or reduce the incidence of respiratory infections. Yet all available evidence shows that the operation neither prevents nor significantly reduces the incidence of these troublesome ailments. Gafafer,[15] in 1932, observed no significant difference with respect to the frequency, severity, or type of attack of disease of the upper respiratory tract in tonsillectomized and nonoperated persons.

A pioneer study of the effect of T and A on the health of children was reported by Kaiser in 1931[16] and again in 1940.[17] He compared the health of 2 groups of children. One group had had the tonsils removed, the other had been recommended for T and A but, for one reason or another, had not been operated on.

Kaiser, in a 10-year follow-up study, observed a reduction in the frequency of tonsillitis and sore throat after operation which persisted during the entire period of study. For a period of 3 years after operation, the surgically treated children enjoyed greater freedom from colds but during the next 7 years the children who had had operations actually had more colds than the unoperated group. Kaiser concludes that, on the whole, the children who were operated on showed only a slight advantage over the unoperated and that the advantage could not be considered statistically significant.

The incidence of pneumonia and bronchitis was greater in the tonsillectomized than in the nonoperated group.

A major source of error in Kaiser's work was that he had to rely on evidence given by the parents. This source of error has been eliminated in the more recent studies.

A careful study of the effect of T and A on the health of 909 girls from well-to-do families attending a large boarding school in England was reported by Paton,[18] in 1943. Fifty-seven per cent of these girls had had their tonsils removed. In 57 (6.3 per cent) the tonsils alone had been removed and in 24 others (2.6 per cent) only the adenoids.

Pharyngitis was equally common in the operated and nonoperated group. Common colds were more frequent among the tonsillectomized. Pneumonia and pleurisy were rare in both groups but were more frequent in the operated group.

Though tonsillitis was less frequent in the operated group, acute bronchitis was more frequent and caused more days lost than were gained by freedom from tonsillitis. Removal of tonsils alone protected against tonsillitis but seemed to be responsible for an increase in respiratory infections. Adenoidectomy seemed to reduce the liability to the usual respiratory infections but it increased the susceptibility to acute otitis media and failed to prevent recurrences.

As part of a study of respiratory illness in two communities in Westchester County, N. Y., Mertz[19] visited families every 28 days during 3 school years, September to June, 1946-1949, and inquired about acute respiratory illness during the preceding 4 weeks. Acute respiratory disease included head colds, colds without sore throat, tonsillitis, septic sore throat, colds with chest involvement such as tracheitis and bronchitis, and influenza or grippe. Patients were divided by occupational class, sex, and age. The communities are prosperous ones and a high order of medical care could be expected.

Mertz found that the incidence of respiratory disease in each of the groups was similar regardless of whether or not the tonsils had been removed. Tonsillitis and sore throat accounted for 3 per cent of the total respiratory illness. In the 5- to 18-year-old group these two conditions were about one and one-half times as frequent in the children with tonsils as in those whose tonsils had been removed. After 19 years of age, the incidence was about the same in both groups. Disabling respiratory illness, that is, illness which caused an interruption in the usual daily work or activities, was similar in frequency whether the tonsils had been removed or not. After age 40, individuals with tonsils removed had a higher incidence of disabling respiratory illness.

The relation of T and A to the frequency of common respiratory infections was studied by McCorkle, Hodges, Badger, Dingle, and Jordan.[20] No differences were found in the age-specific as well as age-adjusted rates for common respiratory infections in children with and without tonsils.

During the course of the study, 26 children had their tonsils removed. A comparison of the actual number of respiratory infections for 3 years after tonsillectomy and the expected number of infections had they not been operated on showed that T and A did not materially alter the average incidence of respiratory infection in this group. The average rate among the 26 youngsters who were operated on had been higher than expected for several years before operation and continued to be higher than expected after operation.

Crookes[21] reported the results of T and A in 50 consecutive operations on doctors' children. The operations were performed over a period of 10 years or so and the results were judged by replies of the physician parents to a questionnaire. He found a reduction in the incidence of tonsillitis and sore throat, otitis media and deafness, cervical adenitis, colds, nasal obstruction, nasal discharge, chest infections, and cough. General health was improved in 35 out of the 50 children. The results are far and away the most favorable in the literature. The study suffers from the lack of a control group, failure to consider the age factor in the changing incidence of respiratory infections, and reliance on the reports of parents, often gathered several years after operation. If the study proves anything at all, it is that doctors are as gullible as anybody.

Otitis Media.—Reports of the effect of T and A on otitis media are inconclusive. During the 3-year period after T and A, Kaiser[17] found that otitis media was only about half as frequent as in unoperated children of the same age, but during the next 7 years those in the unoperated group fared as well as and even a little better than those operated upon. It is Kaiser's view that the operation benefited the younger children who were subject to otitis media.

Paton,[18] in his follow-up study in adolescent girls at a boarding school in England, concluded that the operation had an adverse effect on ear infections. Adenoidectomy increased the liability to acute purulent otitis media. Recurrent attacks were seldom prevented and primary attacks were more frequent.

In spite of the inconclusive results in the literature, every physician who responded to Wolman's survey listed recurrent or chronic otitis media as an indication for operation and 21.9 per cent recommended *adenoidectomy* alone.

Cervical Adenitis.—In Kaiser's experience, cervical adenitis was favorably influenced by operation. According to Paton, acute cervical lymphadenitis was more frequent in the operated children.

Rheumatic Fever.—Kaiser[17] concludes: "The surgical treatment of the tonsils, regardless of the age of the child, offers no certainty of preventing this infection and apparently does not reduce the number of recurrences. The clinical improvement in many cases has justified the operation, and the somewhat meager statistical data at hand in the Rochester study suggest that fatal carditis was noted less frequently in the tonsillectomized group."

It is no longer customary for pediatricians specially interested in rheumatic fever to recommend T and A as a routine prophylactic measure. Nevertheless, 34 per cent of the physicians surveyed by Wolman considered "tendency to rheumatic fever" as an indication for operation.

General Effects.—T and A had no influence on the weight of the girls in Paton's study. Girls of exceptionally low weight and height were as frequent among the operated as the unoperated groups. As for illness from all causes, the girls who had been operated on averaged somewhat more time lost from school (average, 20.6 days) than did those not operated upon (18.5 days).

Hearing.—Even the most conservative physicians regard a conductive type of hearing impairment as an indication for adenoidectomy. However, many years ago, Crowe and Burnam[22] pointed out that the operation for T and A was inadequate as a method for removing lymphoid tissue about the orifices of the Eustachian tubes or for preventing ear infections, and they advocated irradiation of the hypertrophied lymphatic tissue in the neighborhood of the Eustachian orifices. The patients were first operated on, since irradiation of the nasopharynx is not as satisfactory if carried out in the presence of large masses of lymphoid tissue.

Early reports[23] on the effects of irradiation on hearing were favorable, especially in children. These reports failed to take into account the spontaneous improvement which takes place in untreated children.

Bordley and Hardy[24] studied the changes in hearing acuity following the treatment of nasopharyngeal lymphoid tissue by irradiation. They found that irradiation produces a better reduction in the lymphoid tissues and is more effective for this purpose than the usual adenoidectomy.

An improvement in hearing acuity took place in both the treated and control groups. The improvement was slightly greater in the treated group but it was not large enough to be statistically significant. The authors point out that if one depended on data assembled from the treated group alone (without a control group) a falsely optimistic interpretation of the results of irradiation might be made. They attribute the spontaneous improvement to the normal process whereby lymphoid tissue decreases as puberty approaches; to improved hygiene and care during infections, especially in the study group; and, finally, to the factor of experience in the use of the audiometer by repeated testing.

Evidently, then, even after meticulous reduction of retronasal lymphoid tissue by radiation, the effects on conductive-type hearing losses are equivocal.

Allergy.—Pediatricians, especially interested in allergy, are cautious in their approach to the T and A problem. Dr. Lewis Webb (*loc. cit.*) writes: "Removal of tonsils and adenoids is rarely indicated because of the allergic symptoms alone, i.e., hay fever, perennial rhinitis or asthma. In the main the indications are the same as for any child without respiratory allergy. Improvement of allergic respiratory symptoms does not usually follow operation except when a large adenoid mass is obstructing the retropharynx or when the adenoid is a focus of infection with continued or intermittent purulent nasal discharge. The tonsils and adenoids should never be excised in allergic children during the hayfever season. Removal at this time may favor the development of hayfever or, if the patient already has it, make it worse. *According to my experience over the years, T and A will not prevent ordinary colds in allergic or other children.*"

Dr. Bret Ratner (loc. cit.) expresses similar views. "In an allergic child the tonsils and adenoids should not be removed until the allergic disease is well under control. Otherwise infection of regrown tonsillar and postpharyngeal lymphatic tissue will tend to precipitate asthmatic attacks or aggravate them. If the operation seems essential it should not be done in an allergic child during the spring and summer months prior to or during pollination."

Glaser[25] concludes, from a review of the literature and from his own extensive experience, that a T and A done during the pollinating season may lead to the development of bronchial asthma. The operation, when necessary, should be done during a pollen-free period. Any child requiring a second T and A is an allergic child. Young children, 3 years old or less, with obstructive nasopharynx, are allergic.

Dr. James C. Overall (loc. cit.) states: "About eight years ago, I reviewed the records of 100 consecutive children with asthma seen in private practice who were sufficiently ill to warrant skin testing. For various reasons, 35 of them had T and A. Of the 35, 33 by my as well as the mothers' observations, were worse with their hayfever and asthma after the T and A. The indications for operation in allergic children are not too different from the non-allergic except that they require much more careful evaluation. Too many T and A's are done for 'colds' and for numerous other poorer excuses."

HAZARDS OF T AND A

Mortality.—Cautious surgeons regard the operation for T and A seriously. McKenzie,[26] Surgeon at the National Throat, Nose and Ear Hospital, London, considers hemorrhage to be the greatest danger during operation. It is especially to be feared if there has been a recent throat infection or a peritonsillar cellulitis with secondary peritonsillar fibrosis. He cautions against operating on anyone whose temperature on the eve of the operation is over 99° F.

A danger during recovery from the anesthesia is asphyxia from falling back of the tongue. Hemorrhage continues to be a hazard for 24 hours after operation, rarely later.

Slater and Stephen[27] warn that anesthesia for T and A should not be considered a minor event. The responsibilities of the anesthetist are perhaps greater than with many other surgical procedures. They recommend having the patient come into the hospital the night before the operation, thus making a 2-day hospital stay. The greatest threat is anoxia. Sometimes the cause is cessation of respiration as a reflex response to the irritant vapor. Other mechanisms are obstruction of the larynx by dropping back of the tongue, a narrow aperture between the vocal cords, and reflex laryngeal spasm on withdrawal of the tube. They warn against the use of ethyl chloride which may induce respiratory and cardiac arrest. Before starting the anesthesia, loose teeth should be looked for and extracted, if possible, because of the danger of aspiration.

Dr. E. A. Rovenstine, Professor of Anesthesiology at the New York University Post Graduate Medical School, states (loc. cit.): "Tonsillectomy during childhood is regarded by many as a minor surgical procedure and the task of providing anesthesia is often delegated to junior members of the anesthesia staff. This factor alone has contributed to the morbidity and the acknowledged, although low, mortality.

"The problems confronting the anesthetist during T and A are characteristic of all surgical manipulations that involve the respiratory airways. When these are attacked directly, as they are during tonsillectomy, it is the anesthetist's responsibility to protect the lower respiratory tract from obstruction and from aspiration of foreign material. At the same time he must provide a functioning airway that permits adequate, continuous respiratory ventilation. During tonsillectomy the anesthetist's efforts are handicapped by the presence of the surgeon's hands and instruments, as well as blood and secretions. Furthermore the degree of anesthesia requires the obtundation of pharyngeal reflexes to permit adequate and convenient surgery.

"Considerable patience, skill and time are needed to avoid the psychic trauma engendered by a surgical operation in this age group. Frequently neither is available for reasons of economy in terms of time or income. The psychic distress produced by the operation is not often given its due importance in assessing postoperative morbidity.

"Anesthesia for tonsillectomy is by no means a minor procedure and the morbidity and mortality experienced every year is not insignificant."

In 1954, Beecher and Todd[28] reported the results of a cooperative study of death from anesthesia. The data, gathered during the 5-year period, 1948-1952, at 10 university hospitals scattered throughout the country, consisted of 559,548 anesthesias. The over-all death rate from anesthesia was 1:1,560. This includes cases in which anesthesia was a primary cause or a prominent contributing cause.

It is noteworthy that the study was made in university hospitals chosen for the excellence of their departments of anesthesiology. Had it been possible to obtain accurate data about anesthesias given by the less expert, in smaller centers, or in doctors' offices where the facilities for resuscitation are not readily available, the proportion of deaths would probably be considerably higher.

The highest death rate took place during the first decade. Though they received only 9 per cent of all the anesthesias, 20 per cent of the deaths were in children under 10 years of age.

McKenzie[26] states: "Before the late war the mortality (from T and A) cited for one London centre was 1 in 1,000 but figures do not accurately reflect the difficulties, nor do they record the conditions in small hospitals, where both surgeon and anesthetist may be less skilled than in a main centre." Wolman,[4] basing his conclusions on the replies of physicians to a questionnaire, estimates that the mortality from T and A is about 1 per 1,000 operations. In the United States during the nineteen twenties the number of deaths reported varied from 73 to 116 each year.[29] This amounted to about 15 per cent of all deaths from anesthesia. About the same number of children died each year in England where chloroform was widely used. Gale,[30] in 1951, estimated that about 80 children lose their lives each year in England and Wales as a result of the operation.

In 1954, at the Laryngological Section of the Royal Society of Medicine in London, the opening speaker[31] said that, in 1952, 47 deaths were attributed to tonsillar and adenoidal hypertrophy in England and Wales. In 42 of them T and A appeared on the death certificates. In 10 children, ranging in age from 8 months to 9 years, autopsy revealed, as causes of death, asphyxia from aspiration of blood, cardiac failure secondary to pulmonary collapse, overdistended lungs and mediastinal emphysema, and hemorrhage.

Accurate data on deaths from T and A have been compiled by Dr. Morris Greenberg, Director of the Bureau of Preventable Diseases, New York City (loc. cit.). In order to eliminate the possibility that deaths from T and A are concealed under other diagnostic categories, he investigated all deaths in children one to 14 years of age in New York City where the cause of death might conceivably be related to the operation. Included, for example, in addition to T and A, were deaths from pneumonia, bronchitis, and heart disease. Deaths attributed to such conditions as accidents or cancer were not looked into. In all, 643 deaths were investigated. The charts of patients dying in hospitals were reviewed and notations on tonsillectomies performed during the previous 6 months were recorded. If a child died at home, the private physician was consulted.

Ten deaths were found. The death certificates had given the cause of death as hypertrophied *tonsils and* adenoids with mention of the operation in all but one child. There were 5 additional deaths in children who had had a tonsillectomy from 2 weeks to 3 months previously, but a causal relation between the operation and the death could not be definitely established. Greenberg's data indicate that, in New York City, deaths from tonsillectomy are accurately recorded, if *deaths from hypertrophy of tonsils* and adenoids are included as tonsillectomy deaths.

In the previous 5 years, 1951-1955, 46 deaths from tonsillectomy in children under 15 years of age were recorded in New York City. The total number of deaths from diphtheria, mumps, rubella, scarlet fever, typhoid fever, varicella, and whooping cough in the same period totalled 32. If all ages are included, there were 58 deaths from tonsillectomy and 45 deaths from the other diseases mentioned above.

In New York City, then, from 9 to 10 children under 15 years of age died each year from T and A during the past 6 years. An additional 2 persons, 15 years and over, also succumbed, making a total of about 12 deaths a year.

In Upstate New York, which includes all of New York State except New York City, 70 deaths from T and A were recorded during the 7-year period, 1949-1955, an average of 10 deaths a year.[3] Thus, for the State of New York, as a whole, the total number of deaths from T and A during recent years has been about 22 per year.

Mortality data for the United States, 1950-1955, are shown in Table V. In international listing, deaths are recorded under "Hypertrophy of Tonsils and Adenoids" with and without mention of tonsillectomy or adenoidectomy. Hypertrophy of tonsils and adenoids can hardly be considered a cause of death. Greenberg's study indicates that deaths listed under "Hypertrophy of Tonsils and Adenoids" are probably due to tonsiladenoidectomy.

TABLE V. THE NUMBER OF DEATHS FROM "HYPERTROPHY OF TONSILS AND ADENOIDS" AND "TONSILLECTOMY OR ADENOIDECTOMY." UNITED STATES, 1950-1955*

	HYPERTROPHY OF TONSILS AND ADENOIDS†	WITH TONSILLECTOMY OR ADENOIDECTOMY‡
1950	339	305
1951	317	287
1952	346	304
1953	329	307
1954	254	236
1955	220	206

*Source: U. S. Vital Statistics, Dept. Health, Education and Welfare.
†International List No. 510.
‡International List No. 510.1.

The number of persons dying from the operation in the United States varied from a high of 346 in 1952 to 220 in 1955. There has been a notable drop in the number of deaths during the last 2 years (1954-1955) for which data are available.

The T and A death rates vary markedly from state to state (Table VI). New York, though the most populous state, has less operative deaths than California and Pennsylvania. The highest death rates are recorded for Iowa, Oklahoma, and Colorado. The 3 states with the lowest rates are Connecticut, Massachusetts, and Kentucky.

TABLE VI. STATES WITH HIGHEST AND LOWEST CRUDE DEATH RATES FROM "HYPERTROPHY OF TONSILS AND ADENOIDS." UNITED STATES, 1951-1955. (ESTIMATED FOR POPULATION AS OF 1950; STATES WITH POPULATION OF 2 MILLION OR OVER ONLY)*

DEATHS PER 1,000,000 POPULATION			
Highest Mortality States		*Lowest Mortality States*	
Iowa	3.7	New York	1.4
Oklahoma	3.6	Virginia	1.3
Colorado	3.5	Kentucky	1.2
California	2.7	Massachusetts	1.1
Mississippi	2.3	Connecticut	0.7

*Source: U. S. Vital Statistics, Dept. Health, Education and Welfare.

The distribution of deaths from "Hypertrophy of Tonsils and Adenoids" for the years, 1950-1955, by age is shown in Table VII. Eighty-one per cent of the deaths took place in children and adolescents under 20. The most hazardous time of life for the operation is the first 5 years. Although approximately 3 times as many T and A's are done during the 5- to 9-years age period as during the under-5-years age period (see Table III), the number of deaths in the 2 age periods is about the same. This means that the risk of a fatal outcome is about 3 times as great in children under 5 as in those 5 to 9 years old.

Hingson, Cull, and Witzeman[32] report a disproportionately high death rate from anesthesia among Negro patients of all ages. They call attention to the fact that the skin pigment makes it difficult to recognize cyanosis and pallor. No racial difference in anesthesia death rate was observed by Beecher and Todd[28] in their large series.

Poliomyelitis.—A relationship between bulbar poliomyelitis and tonsillectomy has been suspected for many years. One of the earliest to mention this phenomenon was Sheppard,[33] in 1910.

In 1928, Ayer[34] reported his observations on the relative frequency of bulbar poliomyelitis following tonsillectomy. At the same time, Aycock and Luther[35] were carrying out their extensive studies in Massachusetts and Vermont. Out of a total of 714 patients with poliomyelitis they were able to find 36 in whom the tonsils had been removed within a year of the onset of illness. In 16 of these the attack took place within a month after operation and 9 of these were bulbar. The high proportion of bulbar involvement so shortly after T and A led them to conclude that a causal relationship exists.

TABLE VII. THE NUMBER OF DEATHS FROM "HYPERTROPHY OF THE TONSILS AND ADENOIDS" BY AGE. UNITED STATES, 1950-1955*

	AGE—YEARS					
	UNDER 5	5-9	10-14	15-19	20 AND OVER	ALL AGES
1950	106	120	14	18	81	339
1951	105	111	23	15	63	317
1952	124	129	18	10	65	346
1953	122	135	19	12	41	329
1954	108	89	15	11	31	254
1955	86	86	14	2	32	220

*Source: Vital Statistics of U. S. Department of Health, Education and Welfare.

The conclusions of Ayer and of Aycock and Luther have been amply confirmed. Table VIII, adapted from Aycock,[36] summarizes the studies made by a number of different workers up to the time of his report in 1942 and shows the much greater susceptibility to bulbar poliomyelitis after a recent T and A. Of 170 cases of poliomyelitis occurring within 30 days after a T and A, 121 or 71 per cent were bulbar or bulbo-spinal. Of 45 cases occurring 30 to 60 days after operation the cranial nerves were involved in only 20 per cent.

TABLE VIII. THE TYPE OF POLIOMYELITIS FOLLOWING TONSILLECTOMY (AFTER AYCOCK[36])

	TONSILLECTOMY WITHIN 30 DAYS		TONSILLECTOMY 30-60 DAYS	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
Bulbar	99	58	8	18
Bulbo-spinal	22	13	1	2
Spinal	22	13	30	67
Nonparalytic	20	12	1	2
Unknown	7	4	5	11
Total	170	100	45	100

Additional epidemiologic evidence since Aycock's summary report has been published by Lucchesi and LaBoccetta[37] and by Siegel, Greenberg and Magee.[38] Lucchesi and LaBoccetta found that the tonsils and adenoids had been removed in a significantly high percentage of patients with bulbar and bulbo-spinal poliomyelitis. They regard loss of the tonsils and adenoids, regardless of the time of operation, as increasing the risk of cranial nerve involvement.

The study of Siegel and co-workers was based on 6,524 cases of poliomyelitis reported in New York City over the 6-year period, 1944-1949. Their careful observations showed that the percentage of bulbar paralysis was significantly higher than expected among post-tonsillectomized persons within one month after operation. The results from one to 5 months after operation were suggestive but not conclusive. There seemed to be no relationship 6 to 12 months after operation. They also found a higher case fatality rate during the first 2 months after operation. Their observations led them to conclude further that tonsillectomy predisposes to the development of the clinical symptoms of all forms of poliomyelitis. This was also the conclusion of Faber[39] and of Top and Vaughan.[40]

Further evidence of the relationship between T and A and bulbar poliomyelitis is revealed by the tragic case history of the K family, studied by Francis and his co-workers.[41] On Aug. 22, 1941, 5 of the 6 children of the K family in Akron, Ohio, were operated on for T and A. Four of the children also had teeth extracted. By September 5, 14 days later, the 5 children who had been operated on were acutely ill, they all shortly developed bulbar poliomyelitis and subsequently 3 of them died. The parents and the child who had not been operated upon remained well. At this time, Akron, a city of 270,000, was relatively free of poliomyelitis, only 2 cases having occurred prior to the onset in the K family.

After an extensive epidemiological study, the authors concluded that the source of infection was a cousin from a distant city with whom the children had visited several weeks before the onset of their illness. The K children were carrying the virus at the time of operation and the operation incited invasion of the central nervous system in the 5 children while the unoperated child remained well. The operation seemed to transform a mild infection without clinical manifestations into a severe, highly fatal disease. They regard their observations as confirming the danger inherent in T and A during the season when poliomyelitis occurs even though it is not epidemic in a community.

Sabin[42] was able to produce bulbar poliomyelitis in monkeys by injecting virus into the tonsillo-pharyngeal regions. He found that the tonsillo-pharyngeal region is more sensitive to poliomyelitis virus than, for example, the abdominal cutaneous or subcutaneous tissues. Thirteen out of 16 monkeys, receiving virus injected into the tonsillo-pharyngeal region, developed disease of the nuclei of the cranial nerves, while these structures were affected in only 15 out of 250 monkeys injected elsewhere. He regards the high incidence of the bulbar type of the disease after tonsillo-pharyngeal injection as due to progress of the virus along the local peripheral nerves.

Because he was unable to produce poliomyelitis in monkeys by applying virus immediately to the operative wound, while the disease developed following injection into the tonsillar region, Sabin inferred that, in the human being, bulbar poliomyelitis would develop only when the virus was already present at the time of operation rather than as a result of postoperative contamination.

Septicemia.—In a recent paper, Rhoads, Sibley, and Billings[43] report positive blood cultures after T and A in 28 per cent of a group of 68 cases. The frequency of bacteremia was reduced by intramuscularly injected penicillin for 4 to 10 days before operation. No protection was afforded by shorter penicillin administration or by oral penicillin. Although, in their series, the organisms recovered were nonpathogens others have observed the onset of subacute bacterial endocarditis and septicemia after operation for T and A.[44] It is true that these are rare complications; but, when so many operations are done, the absolute number is probably sizable.

Psychologic Trauma.—In most instances, an operation for T and A represents the child's first separation from the home as well as his first admission to a hospital. Coleman[45] points out that the child, often through some ruse, is brought to the hospital where he is surrounded by strange, white-robed people. His reaction is one of terror and confusion. He is resentful at having been lied to and tricked and he is distrustful of his parents who have deceived him and are now deserting him. The operating room and the anesthetic intensify his terror and his sense of separation.

But even under the most favorable circumstances for a child to leave home and go to a hospital is a disagreeable and frightening experience. The psychologic reaction to the operative situation varies. It is true that most children forget their disagreeable hospital stay quickly and are none the worse for it. But a sizable proportion show alterations in behavior, principally fears, negativism, and family antagonisms. A consequence may be fear and distrust of doctors. Coleman regards the psychic trauma which some children sustain from tonsillectomy to be as much a complication as is postoperative hemorrhage or infection.

Langford[16] has observed that severe anxiety states may be precipitated by the shock of operation. In 6 out of 20 children suffering from anxiety states, the condition was definitely related to tonsillectomies under ether anesthesia. The child as a rule had been poorly prepared for the operation, the anesthetic, and the separation from the parents. The attacks began about a month after operation and 5 of the 6 children described them as being "just like having ether."

Levy[17] was impressed by the number of cases of fears, anxieties, and other symptoms which followed an operative procedure, usually a tonsillectomy. Out of a group of 124 children who had had operations, 25 (20 per cent) showed residual emotional disturbances. Although postoperative symptoms occurred at all ages, they were most frequent in the one- and 2-year-old groups. Levy attributes the greater reactivity of young children to their greater dependence on home and mother, their lack of experience outside the home, and their inability to comprehend what is taking place. In addition, they are poorly equipped to handle anxiety. Unlike older children, they are unable to play out their anxiety with toys, because they do not yet possess the words, concepts, and the skill required. For the young child an operation is a raw and brutal experience, the reason for which he cannot comprehend.

It is of interest that, in Levy's series, 13 of the 25 children who developed untoward reactions after operation had shown no deviations from normal behavior before.

The types of postoperative reaction most frequently observed by Levy were night terrors, fears, dependency, and negativism. Most of the children with night terrors were 18 months of age or younger. In this group the night terrors were all of long duration, extending over months or years. Negativistic reactions occurred principally in children 5 years old or older and consisted of such spiteful behavior against the parents as disobedience, temper tantrums, defiance, and destructive behavior.

Dependency reactions, consisting of clinging to the mother, refusing to leave her side, insisting on knowing where she is going and when she will return home, are so common after operation as to be considered normal. Occasionally, however, the manifestations may be exaggerated to an abnormal degree.

The most frequent fears in Levy's group related to darkness, doctors and nurses, and strange men. He attributes the fear which many children experience in the dark to fear of unknown things that may happen and to fear of being separated from the mother. This latter is directly related to the degree of dependency on the mother and, when severe, may lead to insomnia. The child who has been operated upon may find darkness bad since "they put you to sleep and then bad things happen to you."

THE COST OF T AND A

Only a rough estimate can be made of the cost of T and A to the nation since there are no accurate data on the number of operations performed and since methods of calculating hospital costs vary so widely.

T and A in a hospital requires a hospital bed for 1 or 2 days (1.3 days for children under 10 years, about 1.6 days for older children according to the Metropolitan Life Insurance Company experience[48]), the time and skill of doctors, nurses, and anesthetists, auxiliary help, use of the operating room, and use of equipment and materials. Since the operation is an elective one it is not performed—in New York City at any rate—on week ends or holidays. Therefore beds for T and A are used only 5 days a week or, taking into account holidays, about 250 days a year. Moreover, now that operations are not done during 4 months, June through October, beds for T and A patients are actually used only two thirds of 250 days or about 167 days. Another consideration is that, since the operation is no longer done during the summer months when general pediatric wards are apt to be light but, instead, during the winter months when the beds are likely to be filled with children having infections, the pressure on bed space is greater than ever.

The data of Siegel, Greenberg, and Magee[9] can be used to calculate the hospital space necessary for T and A in New York City in 1949. A total of 53,007 T and A's were done in hospitals. If each child required 1.3 days of hospital stay, this means 68.909 hospital days. At the rate of 167 hospital days per bed per year, it would require the equivalent of a 400-bed hospital merely to care for T and A patients in New York City.

In view of these considerations it does not seem excessive to calculate the cost of a tonsillectomy—regardless of who pays for it—at $100. At this rate the cost of the 53,007 T and A's in New York City, in 1949, would be about $5,300,000. This sum does not include the sizable number of operations done out of the city and in doctors' offices. In 1949-1950, the entire budget for the New York City Health Department was $16,756,329. The people of the City of New York paid for T and A's about one third as much as for maintaining the city health department.

If this sum is prorated for the country as a whole and we assume 1,500,-000 tonsillectomies a year, which means that about 40 per cent of the population has T and A's—a modest estimate—the sum for the country as a whole would be $150,000,000.00.

The Ministry of Health estimates the cost of T and A in Britain at 3 million pounds ($8,400,000) or about 15 pounds ($42) per operation.

The great frequency of T and A is regarded by some as due, in part, to the financial greed of physicians. This may be true in isolated instances but it is not an important general consideration. In England, where the surgeon under the National Health Service gets no fee for service, the operation is as popular—perhaps more popular—than ever. And here, in the United States, the children of physicians seem to be operated on as often as the children of others.

DISCUSSION

Before undertaking any form of treatment the benefits to be expected must be weighed against the risks. There is hardly a therapeutic procedure that is free from a certain amount of danger. The use of this or that agent—or none at all—must be decided by balancing desirable against undesirable effects. In instances where the patient is desperately ill, where the outlook is grave, where the treatment may be lifesaving, even though the procedure is hazardous, its use is generally regarded as justified.

Even here grave errors have been made. Until recently the routine use of high concentrations of oxygen was regarded as essential and harmless for small premature infants. The disastrous effects of the overuse of oxygen in this group are only too well known. Retrolental fibroplasia, a direct consequence of oxygen therapy, had become the first cause of blindness in preschool children. Now that oxygen is used much less frequently and in lower concentrations, not only has blindness on this basis disappeared but we find that premature babies are getting along as well as they did formerly. It is evident that the value of oxygen for the premature infant was greatly overrated. The iatrogenic production of blindness in premature infants stands, along with the psychologic neglect of babies in institutions and the consequent high death rate, as a major error in pediatric history.

In the case of T and A the available evidence points to no benefit whatsoever from the operation in the overwhelming majority of children. Yet it is a hazardous procedure and the data presented here indicate that it is a significant cause of death in children. Here is a "disease"—tonsil-adenoid enlargement or infection—with virtually no mortality, and a therapeutic procedure for it which has a sizable mortality.

The relation of T and A to bulbar poliomyelitis and possibly to other forms of poliomyelitis should make us cautious of the hidden dangers which lurk in any therapeutic procedure. Only a few years ago we learned that transfusion in certain girl babies, by rendering them sensitive to Rh-positive cells, made it practically impossible for them ever to have normal children; and even more recently the transmission of serum hepatitis by transfusion was discovered.

A further example of hidden dangers is the relation between radiation of the upper thorax—often for "enlarged thymus"—and carcinoma of the thyroid in children.[40]

The danger of bulbar poliomyelitis after T and A has been greatly reduced by deferring operation during the months when the disease is prevalent and possibly by immunization procedures. It is quite conceivable, however, that the operation opens the way for other neurotropic viruses with different seasonal incidences. Where the benefit to be conferred by operation is so small the possibility of unsuspected hazards must always be kept in mind.

Almost every active practitioner who cares for children can point to youngsters who have improved in one respect or another following T and A. In some it has been an abrupt cessation of troublesome colds, in others a desired weight gain, in still others relief of obstruction, or termination of a series of otitic episodes. Unfortunately coincidence is a mischievous prankster. We remember the occasional, spectacular success; the numerous failures are forgotten.

At present there is no reason to believe that the incidence of colds is significantly reduced by T and A. Kaiser's observations, made in the 1930's, showed a slight advantage to the operated children during the 3 years after operation but no essential difference over a 10-year follow-up period. No difference in the incidence of respiratory disease was found by Gafafer, Paton, Mertz, or McCorkle and co-workers.

Obstruction—in the nasopharynx or throat—may be an occasional indication for operation. The frequency of allergy as a basis for the obstruction, especially in children under 5 or 6 years old, is insufficiently recognized and should be carefully considered before operation is undertaken. It seems wise to wait until the child is 5 years or older because of the tendency for obstructive manifestations to diminish as the child grows, because the risks attendant upon the operation are relatively great in young children, and because of the adverse psychic effect. It is significant that Kaiser,[17] who takes a more tolerant attitude toward the operation than more recent students of the subject, does not mention obstruction as an indication.

All students of the T and A problem agree that the operation reduces the incidence of tonsillitis and sore throat. However, these illnesses account for only 3 per cent of all acute respiratory diseases.[19] It is common experience to see children have repeated attacks for one or 2 winters and thereafter be relatively free of them. Moreover these infections generally respond readily to antimicrobial therapy.

The findings of Paton[18] that the occurrence of purulent otitis media is favored by adenoidectomy should make one cautious about T and A in children with this troublesome ailment.

The carefully controlled study on conductive-type hearing defects by Bordley and Hardy[24] has removed what is generally regarded as an important indication for T and A. Their laborious observations were made at the same institution where Crowe worked. Crowe found that adenoidectomy failed to remove lymphoid tissue about the orifices of the Eustachian tubes completely and he therefore advocated irradiation after operation. Even after this double procedure, Bordley and Hardy were unable to demonstrate that the improvement in hearing was significantly greater than in control, untreated children.

Too little attention is paid to the finding of Mertz that, after age 40, when health is more precarious than earlier and time lost from work more important, the incidence of disabling respiratory illness in males is higher in the operated than in the unoperated.

The careful studies in the literature, although showing beyond doubt that, by and large, T and A has no favorable influence on the health of children, cannot be interpreted as proving that the operation does not help in certain isolated cases. The operation is performed so frequently and for such trivial reasons that, in any study, the casually decided upon cases far outnumber the children in whom there may be some real indication for surgery. Consequently any real benefit to individual children is obscured.

Bass,[50] in 1934, reported a series of 150 children, in the great majority of whom he had himself decided on the indications for operation and had chosen the surgeon and anesthetist. The most frequent indications for operation were frequent colds, tonsillitis, nasal obstruction, otitis, and cervical adenitis.

One hundred thirty-three of the 150 children seemed to have benefited in one respect or other from the operation. In 7 the results were questionable and in 10 there was no improvement. Bass concluded that the operation has a favorable influence on otitis media and "sinusitis." Nose colds seemed as frequent after operation as before but were not as severe. Rheumatic fever was not benefited.

Among unfavorable sequelae were a 5-year-old girl with unexplained fever for 5 weeks, a 6-year-old girl with a lung abscess requiring operation and transfusion, an 8-year-old girl with otitis media going on to mastoiditis and operation, and a 12-year-old girl with putrid necrosis of the lung. All patients recovered. Despite the skill of the surgeons, 6 children required a second operation.

Bass estimates that about 10 per cent of all children would benefit by T and A. Even when the indications are carefully weighed and the operation is limited to this small group, and even when the operation is performed by well-trained surgeons assisted by well-trained anesthetists the results are not impressive, sequelae are not infrequent, and regrowth of adenoid tissue sufficient to require reoperation takes place.

Fry,[51] an English general practitioner, has recommended 40 children from his own practice for T and A over a period of 10 years. This represents 5 per cent of the children under his care. The principal reasons for operation were recurrent otitis media in 24 children, recurrent attacks of tonsillitis in 10, and parental pressure that could not be resisted in 6. In his experience the 95 per cent of children who were not operated on did not in any way suffer because of it.

The physician will do well to recommend against operation except in very special instances. Certainly there is no urgency about excision of tonsils. No one claims that the operation is lifesaving. Now that antimicrobial agents are available, the discomfort of sore throat and otitis media and the threat of mastoid diseases are quickly and effectively handled. On the other hand, there is a definite risk in the operation, as there is in every operative procedure and in every anesthesia.

Medical practice has erred often in the past. In good part, improvement in medical practice can be accounted for by the discarding of useless and harmful procedures as well as by the adoption of beneficial ones.

The continuance of the practice of indiscriminate T and A is indeed an enigma. We live in a medical era which considers itself "scientific." We like to think that we have rid ourselves of the mumbo jumbo and mystical nostrums of the past and we adopt new procedures only after rigorous testing. Yet T and A, whose uselessness, in the overwhelming majority of instances, has been repeatedly and convincingly demonstrated, retains its popularity with the laity and the medical profession. Would we, on the basis of such tenuous evidence as is available in favor of T and A, adopt a new drug which may be lethal for some 300 persons a year?

SUMMARY

1. Data from various parts of the United States and Britain indicate

the operated children during the 3 years after operation but no essential difference over a 10-year follow-up period. No difference in the incidence of respiratory disease was found by Gafafer, Paton, Mertz, or McCorkle and co-workers.

Obstruction—in the nasopharynx or throat—may be an occasional indication for operation. The frequency of allergy as a basis for the obstruction, especially in children under 5 or 6 years old, is insufficiently recognized and should be carefully considered before operation is undertaken. It seems wise to wait until the child is 5 years or older because of the tendency for obstructive manifestations to diminish as the child grows, because the risks attendant upon the operation are relatively great in young children, and because of the adverse psychic effect. It is significant that Kaiser,[17] who takes a more tolerant attitude toward the operation than more recent students of the subject, does not mention obstruction as an indication.

All students of the T and A problem agree that the operation reduces the incidence of tonsillitis and sore throat. However, these illnesses account for only 3 per cent of all acute respiratory diseases.[19] It is common experience to see children have repeated attacks for one or 2 winters and thereafter be relatively free of them. Moreover these infections generally respond readily to antimicrobial therapy.

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Comments on Current Literature

PREPARATION OF THE HEMOPHILIC PATIENT FOR SURGERY: USE OF ANTIHEMOPHILIC GLOBULIN

The success or failure of surgical treatment in patients with hemophilia depends largely upon the maintenance of a reasonable level of coagulability immediately preceding and following surgery. Since a deficiency of antihemophilic globulin (type A hemophilia, sex-linked in inheritance) accounts for from 75 to 80 per cent of reported cases of hemophilia,[1] care of this type of hemophilic subject has received considerable attention in the literature. The minimum blood level of antihemophilic globulin compatible with effective hemostasis is given as approximately 30 per cent of the average normal plasma level. Hemophilic patients vary in the initial level of antihemophilic globulin in their blood and in the ease with which this level can be raised.[2] Since the AHG activity is increased appreciably by transfusions of fresh blood or plasma, temporary elevation of the AHG blood level of the recipient by this means has been the accepted procedure for improving hemostasis and preparing the hemophilic patient for surgery. Raising the level above 30 per cent of normal for a period covering 24 to 48 hours following surgery is considered essential if postoperative bleeding is not to be excessive.[2, 3] However, certain factors limit the effectiveness of this means of bleeding control. The stability of human AHG is unpredictable, and, in some instances, the transfused blood or plasma may be of little value by the time it is received. While small transfusions of whole blood or plasma will raise the blood level of AHG appreciably (1 to 5 per cent), actually relatively large volumes are required to bring the level to 30 per cent of normal. Maintenance of an effective level is made more difficult by the fact that the half-life of AHG averages from four to eleven hours following administration.[2-4]

These problems, in addition to that of suitable donors for transfusion and of successful storage for maintenance of AHG activity (storage at –30° C., preferable), have resulted in a concerted effort to obtain antihemophilic globulin from sources other than human blood or plasma, which could be prepared and standardized in such a way as to assure a constant supply, of predictable effectiveness and free from serious antigenicity or toxicity. Until recently, such preparations have had the major disadvantage that they were highly antigenic. Within the past few months a number of reports has appeared describing the use of animal AHG in the treatment of patients with hemophilia and in the preparation of the hemophilic patient for surgery, including dental procedures.

The earliest preparations used therapeutically in hemophilia consisted of certain fibrinogen fractions separated from human blood by the Cohn process. While in experienced hands some of these early preparations seemed to give satisfactory results, the lack of a reliable method at that time for the assay of AHG meant that the activity of the preparation could not be estimated. Many of these preparations were ineffective or were given in inadequate dosage. The development of more practical methods for the assay of AHG has been reviewed recently by Rosemary Biggs[2, 4] of the group of investigators at the Radcliffe Infirmary, Oxford, England. She stresses the need for checking the fractionation processes at every stage, and states that in "judging the dose of AHG, it is clearly important to have some reasonably reliable method for its measurement."[2] As this author points out, most of the methods used have depended upon assessing the ability of a given sample to correct the abnormality of hemophilic blood, such as the prothrombin consumption test, or the partial thromboplastin time. More recently, the thromboplastin generation test was used by Pitney,[5] and a modified prothrombin consumption test by Wolf.[6] Each of these tests has been shown to carry some disadvantage. The direct assay method originally described by the Oxford group[7] was considered sufficiently reliable, but is somewhat difficult to standardize and to interpret. Biggs now describes a method similar to that of Pitney which she and her colleagues consider of practical value in the controlled therapy of hemophilic subjects. The method "consists in carrying out the thromboplastin generation test on normal and haemophilic $Al(OH)_3$-treated plasma, and on mixtures of the two in known proportions."[2] Since the samples are mixed and tested undiluted, no provision of factor V is required, this factor being present in both whole-plasma samples. According to the instructions given for mixture and dilution, the dilution curve can be constructed with reasonable ease, and the hemophilic samples tested in less than one hour's time. While the method is not precise, as compared with the earlier Biggs-Macfarlane procedure, it is proposed that this method may prove more readily adaptable for use in laboratories not particularly devoted to work on blood coagulation. The author states that this procedure has proved of great value in the controlled therapy of hemophilic patients. "It appears that the level of AHG is a safer guide to the haemostatic efficiency of AHG than is the prothrombin-consumption test."[2]

A recent report by the Radcliffe Infirmary group[3] presents the results in thirteen hemophilic patients requiring surgery or dental extraction, who were prepared for the surgical procedure and were followed closely in the post-operative period. Animal antihemophilic globulin and human plasma preparations were used. For some years this group of investigators had been impressed with the problem of minimal safe blood levels of AHG, the rate of its destruction in the hemophilic circulation, and by the magnitude of the problem of AHG supply, which must be available for management of the known hemophilics, and for emergencies. Studies on animal AHG, particularly from ox and pig blood, its extraction and preparation, had been under way for some years before the present patients were treated. This material varies in potency from one aliquot to another, but the best preparations were shown to have an activity about 8,000 times that of the same weight of fresh human plasma-protein. However, contamination with fibrinogen and other proteins renders it antigenic, which limits the duration of treatment with a particular animal preparation to from 10 to 14 days and prevents any later use of the same material in the same patient. The first clinical trial with bovine AHG was reported in 1954 by Macfarlane, Biggs, and Bidwell.[8] The subjects of this preliminary clinical trial were three hemophilic patients in need of dental extraction who volunteered to receive treatment with full knowledge that the preparation was still in the experimental stage. All necessary dental extraction was carried out immediately following the administration of the bovine preparation. The results were encouraging: in two of the three patients there was virtually no bleeding after extraction, the tooth sockets healed promptly and completely, and no ill effects arising from the administration of animal protein could be detected. The third case was that of a patient who had been under long-term treatment for a convulsive disorder; this patient showed on admission a lower platelet count than that usually found in hemophilic subjects. In this instance the administration of bovine AHG resulted in a marked thrombocytopenia which persisted for two weeks, but no purpuric manifestations were observed. Treatment with AHG in this patient had been stopped after four days. Nevertheless, the extraction of sixteen teeth was accomplished with remarkably little bleeding. Subsequent investigations revealed that bovine AHG does contain an agglutinin for human platelets, and the toxicity and fate of the injected animal antihemophilic globulin are discussed in some detail in a separate publication by two members of the group, Sharp and Bidwell.[9] Shortly after the preliminary trials in 1954, a serious emergency occurred[3] in which the use of animal AHG was a lifesaving measure. A young hemophilic man, accidentally shot at close range, suffered extensive wounds of the back and left elbow. After three weeks of repeated transfusion this patient was transferred to the Radcliffe Infirmary. The problem was complicated by the fact that he had been sensitized to bovine AHG by the previous administration of a hemostatic agent derived from ox blood (Coagulen). This patient was carried successfully through the necessary surgery by the use of pig AHG. Under hemostatic control by this means, the wounds in the back were grafted with skin removed from the thigh, and a traumatic brachial arteriovenous aneurysm which had developed in the elbow was resected.

The thirteen new patients reported recently,[3] and a fourteenth patient requiring surgery for acute intestinal obstruction, who was admitted to the hospital after the present report had been submitted for publication, were all emergency cases. The authors strongly advocate reserving treatment with animal AHG for such emergencies, since risk of anaphylaxis would deprive the patient of its aid in some possible future crisis. Most of the hemophilic patients treated by this group have been managed by the use of human AHG, or by transfusion. As indicated, the fourteen patients in the present series were dental or surgical emergencies. Many of these patients had a long history of bleeding—hematemesis, melena, hematuria—and some were crippled from repeated hemarthroses. One was a 19-year-old man who had been injured three weeks before in a motorcycle accident and whose face and scalp wounds failed to heal. During this period the patient had received 28 pints of blood and 5 liters of plasma in an attempt to control the persistent bleeding. Under treatment with human and pig AHG, plastic surgery of the face and scalp was accomplished with good result. Likewise, a boy of 15 years was able to undergo surgery involving the removal of laminae from twelve vertebrae for the treatment of a massive extradural clot.

In these patients, antihemophilic globulin concentrated from bovine or pig blood was administered in an average dose of 200 to 400 mg., equivalent in activity to about 2,500 ml. of fresh human plasma. In no case was there abnormal bleeding while the level of AHG in the blood was above 30 per cent of normal. There was, however, among the patients considerable individual variability in the dose required to maintain this level. In the case of clean wounds, the temporary elevation of the AHG level by one or two injections might be followed by complete healing without hemorrhage; in large or infected wounds bleeding might recur, should the AHG level fall below 30 per cent. In all cases, rapid healing took place during AHG treatment. The authors state that these AHG preparations are definitely antigenic, although in most instances mildly so. Skin tests, as a rule, are negative, and no antibodies active against the AHG used could be demonstrated in the recipient's blood. In a detailed study of this aspect by Sharp and Bidwell,[9] the fate of the animal AHG was determined by fluorescein-conjugated antisera. Evidence was obtained which suggests that the protein fraction is concentrated in the wound fibrin of the recipient. In two summary articles,[2] one a presentation before the Section on Medicine, Royal Society of Medicine, Biggs outlines details of the assay of AHG, tests for its potency in AHG preparations and in the patient's blood, with emphasis on the management of the hemophilic patient.

In the light of their experience the Oxford investigators stress the value of animal AHG, at the same time emphasizing the necessity of caution in its use. Hemophilic patients referred for surgery should be evaluated carefully. Where actual surgery is required, but where the areas of expected hemorrhage are superficial, or readily accessible, control of bleeding may be accomplished by mechanical means alone. In the case of certain surgical procedures, in which healing may require only two or three days, the use of adequate amounts of human plasma is suggested, reserving the animal AHG for possible future use. In the case of major surgical procedures in which bleeding areas may be extensive, the use of AHG from bovine or pig blood is recommended. Since antigenicity manifests itself in from ten to fourteen days as a rule, the specific animal AHG used should be discontinued at this time, or before, if signs of antigenicity are apparent, with change to the other animal AHG or to human plasma or AHG concentrate. No cross-antigenicity between bovine and pig AHG has been observed. In some instances a combination of animal AHG and human plasma was administered. These workers recommend that assay of the AHG level in the patient's blood be carried out before treatment and at frequent intervals during convalescence from surgery; they advise special care in order to prevent excessive movement or inadvertent trauma of affected parts following surgery, including the use of special dressings, protective devices for the gums in the case of extensive dental procedures,[10] etc. The authors look forward to the "production of a highly potent, non-antigenic antihaemophilic factor . . . which, like insulin and other animal organ extracts, might be active without causing sensitisation."[3]

RUSSELL J. BLATTNER

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Correspondence

[The letter of Dr. Tabrah in the issue of last December has brought considerable correspondence to the Editor's desk. Several of the discussions follow.]

To the Editor:

I have been following your correspondence and the editorials concerning the pleasures and the displeasures of pediatric practice. For seventeen years I have done general medical work. This year, at 46, I am giving up a lucrative practice, a lovely office and forfeiting my savings to take two years of training as a pediatric resident. As the years have passed all of my dealings with the adult patient have grown more and more boring. At the same time my fascination with children, sick and well, has grown. It had not occurred to me that there were those in pediatrics who found no pleasure in anything other than the so-called ''interesting'' cases, the pediatric problem cases, etc. I had not conceived of pediatrics as being divided into the interesting work of the academician as contrasted to the dull monotony of general pediatric practice. In my own practice my metamorphosis from general work to pediatrics has been brought about by a process of natural selection. I recognized long ago that the trivialities constituted a large part of pediatric practice. This makes it no less interesting or, if you will, any less worth while. I have always felt that it kept me more on my toes—alert to the fact that a fever may be due to a cold, but that it might bear watching lest it bode something more fearful. Personally, I could not bear the strain of constantly being personally responsible for the care of a host of seriously ill and dying ''interesting'' cases. The laughing, rowdy well child who is brought in only for his polio shot is a delightful part of the practice of pediatrics.

Perhaps formal training in pediatrics in some institutions gives to its students the concept that pediatrics deals only with fascinating illnesses in children. Experience in general medical practice instills another concept, namely—pediatrics deals mostly with well children or those whose illnesses are trivial. I am sure of this. I have records which will substantiate it. Parent counseling, well-child care, community work in affairs of children, management of trivialities—these things take up more of the average practicing physician's time than the diagnosis and treatment of the medically exotic. The doctor who does not find all of these things interesting is bound to find the general practice of pediatrics boring.

Reasoning along these lines I have refused to allow myself to be discouraged in my plans. The first article which appeared in *Medical Economics* along these lines only made me more determined to pursue a delayed career. The crepe which has been hung in the pages of the journals has left me cold.

Perhaps I am wrong—I will let you know in about two and a half years!

KEITH HAMMOND, M.D.

Paoli, Ind.

To the Editor:

I have read and reread the letter from Dr. Frank L. Tabrah. I agree with you that the "dissatisfaction" in Dr. Tabrah's case probably lies more in his own personal characteristics than in what constitutes present-day pediatric practice, and that this is true in many other instances. His letter, however, brings up some questions relating to practice and to education and training not answered by Lee Hill's statement, from the standpoint of the "Board," nor by my editorial.

Dr. Tabrah is obviously in earnest about the matter, as have been several young pediatricians who have discussed with me similar dissatisfactions. One wonders what their motivation was in choosing pediatrics as a specialty and why it was that they had not realized the nature of the work they would be doing until after they had actually entered practice. It is not likely that their basic personality could be greatly altered by the type of medical education they got nor by their hospital training except in so far as their attitudes and sense of values were influenced by the character of their teachers. But is it not possible that pediatrics could have been presented to them in such a way, somewhere along the line, that they would have had a clearer picture of what to expect from practice, and could not the well child and the factors which influence his total health and welfare be so presented that this would be a fascinating field full of challenge to an intelligent and inquiring mind? If this had been done for Dr. Tabrah he could hardly have written "Well babies still frequent the pediatrist's office, but it is inconceivable that any physician with intelligence and interest in the unusual can long survive the routine of playing grandmother for years on end in a well-baby practice," or make the statement about "the boredom of viewing the medical world from the inside of a diaper," or of making prospective pediatricians aware about the "enforced preoccupation with trivia largely unrelated to disease" in pediatric office practice. There are plenty of examples of affective teaching that could have changed this attitude. I think of the newborn. Nearly all newborns are normal and yet when the subject is properly presented and interest stimulated it opens up an immense field for investigation. In recent years such investigation has led to a great deal of valuable new knowledge. There is still much to learn about children of every age group. Interesting phenomena are by no means all associated with disease. The basic facts of all aspects of growth and development are appreciated only by knowledge of the normal. The whole field of child welfare centers around this knowledge. It is quite clear that improvements in education and training along this line are needed. In other words it is the child himself who needs to be appreciated by the physician if he is to derive full satisfaction from pediatric practice.

Another feature of education and training which could be helpful in preparing prospective pediatricians for the type of practice they must expect to have is greater and more effective use of outpatient departments. In many training centers this facility has been inadequately used. The hospital wards with their bizarre and unusual cases and difficult diagnostic problems are featured. The trainee needs this training but he also needs to see the more common and ambulatory patients and to have equally good supervision and teaching in regard to these patients as he gets on the wards. Only rarely is this the case, and he goes into practice expecting the kind of patients he learned about on the wards. He is unhappy because he seldom encounters them and is ill-at-ease in the presence of the more common problems about which he has had little training.

Most pediatricians adjust to this situation in practice rather quickly and spontaneously, largely, I believe, because of personal characteristics and inherent interests and values. The results of the survey published in *Medical Economics* last November indicating that two-thirds of the practicing pediatricians were satisfied with their choice of a specialty bears out this fact. However, the dissatisfaction of the other third needs thoughtful consideration. Dr. Tabrah's letter points out some of the problems that face us. One is economic in nature; the high financial overhead of maintaining an office can be met only by seeing large numbers of patients, and this assembly-line type of practice robs him of most of the interesting and rewarding features of pediatrics. The result is boredom and frustration. Neither the pediatrician nor his patients benefits adequately from such practice. Furthermore, he has little if any time to devote to such self-improvement activities as teaching and hospital staff duties and assignments. He finds himself in a competitive merry-go-round without academic status and a minimum of specialist or consultant status, unless he has, by good fortune, had training in a pediatric subspecialty.

ARTHUR H. PARMELEE, SR., M.D.
Los Angeles, Calif.

To the Editor:

Pediatrics: Its Own Reward?

"The reward of a thing well done," wrote Emerson, with economy of words, "is to have done it.''* This quote, Mr. Editor, introduces my two cents' worth into the discussion sure to be elicited by Dr. Frank Tabrah's letter in the December issue of the JOURNAL OF PEDIATRICS. Poor Dr. Tabrah withdrew, rather than retired, from the private practice of pediatrics at an early age, because, in Hamlet's phrase, it seemed to him weary, stale, flat, and unprofitable. Now I am sure that, like myself, Dr. Tabrah must agree with Dr. A. H. Parmelee, Sr., that no one goes into pediatrics to get rich. That disposes of Hamlet's last adjective.

But to Dr. Tabrah, ''Pediatric medical office practice is not enough; there are too many private pediatric practices being started today that will be abandoned from sheer boredom.'' And earlier in his letter the doctor writes ruefully, ''A few years ago this colorless job was relieved by challenges of frequent and severe disease, and the physician was called upon to exercise his greatest ingenuity.''

Why not say, ''Pediatrics and preventive medicine have been altogether too efficient. 'Fie upon this quiet life! I want work!' '' (Shakespeare again.)

Dr. Tabrah says, ''There are no longer enough surprises in the package.'' And his general implication is that simplification of infant feeding, greater knowledge of vitamins, of antibiotics, have reduced him and his bored colleagues to ''preoccupation with trivia largely unrelated to disease.''

Now, boot-licking editors has never paid off. But here's an accolade to you for having the imagination to reprint in your column Dr. Parmelee, Sr.'s excellent editorial from the *Bulletin of the Los Angeles Children's Hospital*, on ''Pediatric Rewards.'' Pediatrics needs men like Dr. Parmelee, who can see ''the spirit pushing in a blade of grass . . .'' or in a normal child. Pediatricians are needed who can individualize, to whom each upper respiratory infection is a *ding an selbst*, to whom unthinking routine is anathema. We must be able to stop short in the midst of office hours with scheduled appointments, to spot a newly born infant with hitherto unsuspected congenital dislocation of the hip, or to ''run down'' a heart murmur which may have been missed, leading perhaps to the discovery of an operable lesion.

Excitement? In every field, in every age, it is born of responsibility. The engineer at his throttle, the captain on his bridge, the pitcher on his mound, the mother beside the crib, the health commissioner in the midst of an epidemic, all must and do often feel the excitement of a job well done for those who depend upon them, of mistakes avoided which could so easily have been made. In pediatrics especially, experience itself can be exciting if one is determined that past mistakes shall not be repeated, that future babies shall benefit rather than suffer from them.

Annoyances? Who can deny that in pediatrics these abound, and in perfusion? Chief of these, of course, is the ever-ringing, never-convenient telephone. Worst of all, the irritation incidental to it must *not* be transmitted to the anxious mother whose confidence in the doctor has led her to call him in the first place, and whose question is not trivial to her, although it may sound so to him.

Thirty-five years of telephonic exhaustion, plus undue interest in teaching and writing, led, or forced, me to retire from the *private* practice of pediatrics at the early age of 64. ''Disgruntled?'' (to use Dr. Tabrah's word). Yes—with my own inability to adjust to the unavoidable; but not with pediatrics, nor with babies, nor even with their clamorous elders.

But bored? Impossible! Dr. Tabrah waxes graphic over the ''boredom of viewing the medical world from the inside of a diaper.'' To answer him in kind, I have always found diapers quite absorbing, and early learned from Dr. Holt, Sr., the importance of their contents.

Happily for me—and this is pertinent only as it indicates that my pseudo retirement has no etiology in ennui nor in lack of interest—I continue in the department of pediatrics at Washington University and work half-time in the clinic at Homer G. Phillips Hospital and as director of its Department of Pediatrics. Children's Hospital Conferences, plus a well-baby clinic, round out my week. I am seeing more infants and children than I ever did in private practice. The remuneration accorded the above has served to make my door at least unattractive to the ''wolf.''

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*"The New England Reformers"

By Professor George Herbert Palmer's standard,* a pediatrician is indeed a professional man: "Every sound professional man, every sound teacher at least, is engaged in his work for the fun of the thing. . . . 'To this end was I born and for this cause came I into the world,' said the greatest of Teachers. . . . The compensation of the professional man is measured by his inner outgo, and not like the tradesman's by his external income. . . . Conscious of our powers, we see in some profession an opportunity to exercise them, and to it we turn with an eagerness which gives zest to severe toil."

PARK J. WHITE, M.D.

St. Louis, Mo.

[The following letter was too lengthy to publish in full. Excerpts have been selected by the Editor.]

To the Editor:

I agree that present-day child-care medical training facilities offer little to prepare either general practitioners or pediatricians for the office care of children. Training is weighted on the side of the unusual, particularly unusual physical deviations. The importance of this training is not to be minimized, but it is unfortunate that dealing with new and unfolding life is not made to seem important and exciting. It is also unfortunate that pediatricians go out only superficially trained and stimulated to fulfill their role in simple everyday well-child care. The distaste is understandable because most of the teaching is done by those who are only interested in the physically ill child. The child is too often seen as an interesting disease rather than an exciting unfolding personality living in a family constellation. As a result, many young men while in training have never seen a pediatrician in any other role than as a bedside consultant. This phase of child care has been aggrandized to the exclusion of the pediatrician's important role in shaping the oncoming generation through well-child programs.

The public's and our interest has largely been on the physical side, but the public also warmly responds to whatever we will offer on the side of preventive psychiatry. Few psychiatrists have had an opportunity to put their theories to a test in everyday living experiences with the growing child in a family constellation. Yet increasing numbers of pediatricians are learning from experience that certain principles in the area of emotional development have a predictable verity just as principles we have come to take for granted in physical care have a predictable, constant validity.

To have a new life in a new family entrusted to one's care is an ever-changing, ever-exciting, highly varied, and challenging experience if one sees life to be intrinsically interesting. Who else has the enviable position of the pediatrician? The general practitioner spreads himself too thin to ever become oriented to a really comprehensive well-child program. If the pediatrician sees many very ill children, their care will soon be at the expense of his well-child program. Therefore, perhaps ideally, many men are needed to care for a large number of well and a relatively small number of sick children.

Maybe the specialty as it is taught from the ivory tower represents only a small fraction of the real role of the pediatrician in society. I hope to be privileged to care for the physical ills of children in the future, but, if I do not, I will look forward to endless discussions with endless mothers, and every new mother and every new child will afford endless surprise packages to keep life interesting for me.

Dr. Tabrah's letter is thought-provoking and valuable. I think we need periodical reappraisals of our roles. Especially we need to help our young men know that their training experience is not a picture of future practice. Few who seek that role will have an opportunity to fulfill it, but out in the stream of life there are satisfactions and adventures never thought of during the years of training. I hope I have lifted the curtain a little so that those who are interested may see a little of a side of pediatrics that probably no training program could adequately provide.

I like the work I do.

CHARLES A. TOMPKINS, M.D.

Omaha, Neb.

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*Palmer, G. H.: Trades and Professions, Houghton Mifflin Co., 1915, pp. 14, 15.

News and Notes

The following diplomates were certified by the **American Board of Pediatrics, Inc.**, at Boston, Massachusetts, December 6, 7, 8, 1957.

Dr. Richard M. Auld, 809 Viers Mill Rd., Rockville, Md.

Dr. Jerome Bernstein, 542 Maplewood Ave., Bridgeport, Conn.

Dr. James Edgar Boyland, 9416 Byeforde Rd., Kensington, Md.

Dr. Sidney Brodie, 24 O'Rourke Path, Newton Centre, Mass.

Dr. Paolo B. Bucci, 104-19 102nd St., Ozone Park, N. Y.

Dr. William Roderick Buchanan, Jr., 86 High St., Greenfield, Mass.

Dr. V. Jane Smiley Burgoon, Matson Ford Rd., Conshohocken, Pa.

Dr. Glen Garth Cayler, 221 Gerry Rd., Chestnut Hill, Mass.

Dr. Harold Patrick Charbeneau, 708 Monitor-Leader Bldg., Mt. Clemens, Mich.

Dr. William D. Cochran, 280 Montauk Ave., New London, Conn.

Dr. Robert Swan, Cooper, 1719 Crooks Rd., Royal Oak, Mich.

Dr. Anthony J. Cuti, 53 Harrington Ave., Lindenhurst, N. Y.

Dr. Joseph D'Agrosa, 15 Railroad Ave., Patchogue, N. Y.

Dr. James Arthur Davis, Jr., 5810 Chevy Chase Parkway, Washington, D. C.

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Dr. Raymond S. Duff, Newton Road, Woodbridge, Conn.

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Dr. David Kligler, 175 Bryant Ave., White Plains, N. Y.

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Dr. Morris William Rosenthal, 8561 Long Point Rd., Houston, Texas

Dr. Joseph Gerald Rossi, U.S. Naval Hospital, Philadelphia, Pa.

Dr. Arthur J. Salisbury, 203 Commonwealth Ave., Boston, Mass.

Dr. Raymond E. Schipke, 18 Briarwood Rd., West Hartford, Conn.

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Dr. James Burnley Wood, 1459 Rutledge Ave., Charlottesville, Va.

Dr. Sumner Root Ziegra, 2 West Shore Drive, Massapequa, N. Y.

SPECIAL FOREIGN CERTIFICATES:

Dr. Luis M. Mabilangan, 840 South Wood St., Chicago, Ill.

Dr. Sayanapuram Nagaswami, Plot No. 398B, First Trust Main Rd., Mandavalli Pakam, Madras 28, India

Dr. Horacio Padilla Muñoz, Av. Niños Heroes No. 961, Apto. 1, Guadalajara, Jal., Mexico

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Handbooks on Fluoridation Available for Community Use.—To aid in community education on water fluoridation, the Committee to Protect Our Children's Teeth, citizens' group headed by Dr. Benjamin Spock, is making available two handbooks.

Our Children's Teeth is a 104-page digest of expert opinions on various aspects of fluoridation, designed to serve as a handy basic reference source. Authors include Dr. Herman E. Hilleboe, New York State Health Commissioner; Dr. H. Trendley Dean, Secretary, Council on Dental Research, American Dental Association; Dr. Thomas Parran, Dean, Graduate School of Public Health, University of Pittsburgh, and former Surgeon General, U. S. Public Health Service; Dr. Robert A. Kehoe, Director, Kettering Laboratory; Dr. Reidar F. Sognnaes, Professor of Oral Pathology, Harvard University, and Dr. Detlev W. Bronk, *President*, National Academy of Sciences.

The volume includes a statement by leading American authorities on human nutrition, an explanation of the chemistry of fluorine by the nation's foremost chemists, a chronology of the fluoridation movement, summary of experience in major cities, a statement on the legality of fluoridation and a roster of national organizations supporting the measure.

Gains and Setbacks is a digest of experiences in more than thirty communities, designed as a guide in the planning of a public education campaign. It includes articles by public health authorities and experts in mass communications as well as a U. S. Public Health Service report on the status of fluoridation throughout the country, a summary of court action on the measure and a comprehensive directory of source material.

Both books may be ordered from the Committee to Protect Our Children's Teeth, 105 East 22nd Street, New York 10, N. Y. *Our Children's Teeth* is priced at $1.00; *Gains and Setbacks* is priced at $1.50.

The **Third International Congress of Allergy,** sponsored by the International Association of Allergology and French Allergy Association, will be held in Paris, France, Oct. 19-26, 1958. The program will consist of symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, autoimmune reactions, dermatology, and socioeconomics aspects; sectional papers, limited to 10 minutes, on any phase of allergy; and round table conferences on selected subjects led by international authorities.

For all information regarding the program and papers to be presented, please write to:

United States and Canada: Dr. Samuel M. Feinberg, 303 East Chicago Ave., Chicago, Ill.

Latin America: Dr. José M. Quintero Fossas, Paseo 313, Vedado, Havana, Cuba.

Europe and other countries, and for Congress information and registration: Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris 7, France.

The **Harvard Medical School** announces a postgraduate course in general pediatrics, June 2-13, 1958, and in pediatric metabolism and endocrinology, June 10-13, 1958, at the Burnham Memorial for Children, Massachusetts General Hospital, under the direction of Allan M. Butler, M.D., and Nathan B. Talbot, M.D. Enrollment may be for the entire course, or for the last four days. For further information, write to Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.

The **Department of Pediatrics, Baylor University College of Medicine,** Houston, Texas, and Division of Maternal and Child Health, State of Texas, March 10, 11 and 12, 1958, will conduct a Pediatric Symposium at the Texas Children's Hospital Auditorium, Texas Medical Center, Houston. Guest speakers to participate will be: Robert A. Aldrich, M.D., of Seattle, Louis K. Diamond, M.D., of Boston, Robert A. Good, M.D., of Minneapolis, Jack Metcoff, M.D., of Chicago, Robert E. L. Nesbitt, Jr., M.D., of Albany, N. Y., and Douglas N. Buchanan, M.D., of Chicago.

Books

Rio Grande Medicine Man. M. K. Wylder, M.D., Santa Fe, N. Mex., 1958, Rydel Press, 186 pages. Price $3.75.

This is an unusually interesting and, in many ways, a fascinating book. Dr. Wylder, of Albuquerque, respected and admired by his pediatric colleagues throughout the country for his work for children in New Mexico, has written some of his reminiscences of an active practice of over fifty years. It is, however, much more than an interesting and at times amusing collection of incidents and stories. Parts of it are real Americana. It reflects, moreover, the philosophy and work of a physician who represents the finest type of practitioner. Without the author ever calling attention to it, the reader senses the code of the physician's duties and responsibilities to his patients by which he has lived, his tolerance for and understanding of human weaknesses, and his sympathy for the unfortunates. The book has been brought out locally by the author, but it deserves a much wider reading. Lay readers as well as physicians will enjoy it. Some of our social workers may be a little shocked by his activities in placing children for adoption, but knowing Dr. Wylder we doubt if any social agency has ever had a better record of satisfactory placements. His reference to the 7-month premature babies who, in seclusion, gain 4½ pounds in the first month of life, brought back some memories of similar phenomena in our own practice, which, like Dr. Wylder, we had wiped out of our minds. This is an example of "abnormal growth" not found in any textbook, nor inquired into by the Board. To many present-day practitioners, who resent a house call only a few blocks away from home, Dr. Wylder's description of some of his trips into the mountains in his early days of practice will be almost unbelievable. Yet we are sure that he has had a much fuller, richer, and happier medical life than most of the men in practice are having today.

B. S. V.

The Volunteer. David L. Sills, Chicago, 1958, The Free Press, 320 pages. Price $6.00.

A report of the Bureau of Applied Social Research of Columbia University. The author in an attempt to find the motivations, attitudes, and reactions of the volunteer membership and workers in a national health agency selected the National Poliomyelitis Foundation for study and analysis. In its concept and scope therefore, the study is limited to one segment of the thousands of volunteer workers in health organizations. This makes the title misleading, as it is not a general study of the ''volunteer,'' but rather a study of the volunteer worker in the Polio Foundation. This takes away from its importance as a social study, as valid general conclusions applicable to "The Volunteer" cannot be drawn from a study limited to a single organization. Although rather verbose, the report is of interest to physicians. A careful editing of the material combined with considerable cutting would have made for better reading. There is inadequate discussion of some important matters that concern the volunteer, as for example of the emotional attitude of the ''polio volunteer'' created by the type of publicity developed by the ''corporate organization,'' or central headquarters of the Foundation. This, beyond question, has had a tremendous influence on the reactions of the volunteer worker at the chapter level and has been a subject of discussion among the volunteer workers of other health agencies with objectives involving diseases of greater medical importance than poliomyelitis. While it may give a fairly accurate picture of the volunteer worker in the Foundation, his motives and attitudes, its findings must be interpreted with caution and reservation if the attempt is made to look upon them as reflecting the volunteer worker in all agencies as the title implies. In the interviews with ''polio volunteers,'' which are given in considerable detail and selected by the author, organization comparison favorable to the Foundation is very much emphasized. This left the reviewer with the feeling that the author was not entirely objective in the study, presentation of the report, and conclusions, as similiar critical comparisons, but unfavorable to the Foundation, undoubtedly would have been made if the volunteer workers in some other health organization had been interviewed. Complete objectivity is an essential attitude in a study or report if it is to be of any value or importance beyond propaganda. As the report will in all probability be referred to frequently in the coming months, these limitations as to the scope and value should be kept in mind.

The Incurable Wound and Further Narratives of Medical Detection. Berton Roueché, Boston, 1957, Little, Brown & Co., 177 pages. Price $3.50.

To those who are unacquainted with his previous book, *Eleven Blue Men,* let it be said that Mr. Roueché is perhaps the best writer of our times when it comes to presenting medical topics to a lay audience in an interesting and accurate way. The subtitle ''narratives of medical detection'' describes his method or form of presentation. The present volume is a collection of a half dozen stories that have appeared in the *New Yorker.* The story of "The Incurable Wound," relates the discovery of the transmission of rabies by bats in the United States. "The Most Delicate Thing in the World" is a splendid description of the work of the Poison Control Centers established in many cities in the last four years, and fine publicity for the crusade against accidental poisoning started by the pediatricians. The story of the side effects of cortisone in producing manic-depressive symptoms in a man given the drug for the treatment of periarteritis nodosa, is one of the most vivid pieces of descriptive medical writing we recall. While written by a layman, it belongs in the group often referred to as "compulsory reading" for the medical student and practitioner. The medical profession is fortunate in having a writer with the ability to present intricate medical subjects to the public, not only accurately and ethically, but in a form that makes fascinating reading. It is highly recommended for the physician as well as for lay reading.

B. S. V.

The Dermatologists' Handbook. Ashton L. Welsh, Springfield, Ill., 1957, Charles C Thomas, 426 pages.

This is a comprehensive, clear, up-to-date manuscript of great value not only to the dermatologist, but also to those physicians engaged in related specialties, particularly the pediatrician, the internist and the general practitioner. The first portion of the book contains detailed descriptions of the many drugs employed in topical applications to the skin and mucous membranes. It stresses the indications for and usages of lotions, ointments, creams, powders, wet compresses and other modalities employed for relief and aid to the inflamed or diseased skin surface. The descriptions of the sources of various medicaments, their incompatibilities and their sensitizing properties are rightfully stressed.

The second portion of the book is of equal importance because it deals with the systemic and prophylactic therapy of dermatologic disorders. It describes the close relationship of the skin to other organs in that disturbances of certain systems may be manifested by skin lesions and conversely that dermatoses of long duration and epidermal infections may produce systemic effects. An important lesson stressed by the author is that the dermatologist must have thorough knowledge of systemic physiology and disease and of their relationship to the skin.

An extensive review is given of the numerous drugs used orally or parenterally for systemic effect and a chapter is devoted to the description of adverse reactions produced by certain drugs.

C. W. L.

Radiology of the Alimentary Tract in Infancy. Roy Astley, M.B., M.R.C.S., D.M.R., London, 1956, Edward Arnold (Publisher) Ltd., 287 pages. Price $10.00.

This publication is a noteworthy contribution in the rapidly advancing field of pediatric radiology. It should serve the pediatrician, pediatric surgeon, and radiologist equally well, being as it is a compendium of information relating not only to the gastrointestinal tract but also to the adjacent structures and viscera. Descriptions of the normal are purposely omitted, the net result lending itself to either quick reference or more leisurely perusal. The subject material, of course, ranges from lesions of the pharynx and esophagus distally segment by segment to the anus, and "while the main concern is the baby during the first year of life, there is not infrequent excursion into the second year or even later when it illustrates some practical point" (e.g., duplications, pneumatosis intestinalis). The author has interested himself specifically in the esophagogastric junction and diaphragm, one of the more controversial of subjects among pediatricians, surgeons, and radiologists, taking issue for instance with Neuhauser and Berenberg on the subject of chalasia. His views on such entities as rumination, pylorospasm, congenital esophageal varices, chylous ascites, and partial thoracic stomach—to mention a few—are always informative and challenging although not uniformly acceptable. In brief, this volume should be available to all physicians attempting the management of diseases of infancy.

H. A. H.

Editor's Column

THE JOURNAL OF PEDIATRICS EDUCATIONAL FOUNDATION

A corporate organization of the Editorial Board, *The Journal of Pediatrics Educational Foundation,* has been chartered under the Missouri nonprofit organization law. Its purpose is to simplify and facilitate the handling of the *Journal of Pediatrics Fund* established by the publishers of the JOURNAL, as announced in the issue of last December, and whose use "for the furthering of pediatrics" is the responsibility of the Editorial Board.

The educational purposes of the Foundation have been broadly stated and permit the use of its funds for Lectureships, Fellowships, medical research, etc., in the field of pediatrics, as may be decided upon by the Editorial Board.

The By-laws of the Foundation provide for three Directors. Two of these are appointed by the Board and one by the publishers. Their function is to manage the Foundation funds, keep records and accounts, and make expenditures as instructed by three Trustees. The Trustees are appointed by and must be members of the Editorial Board. Their function is to carry out the use of the Fund as decided upon by the Board as a whole.

The following appointments to the Foundation have been made:

Directors: By the Editorial Board, Alexis F. Hartmann, Borden S. Veeder.

Directors: By the Publishers, Joel A. Rogers.

Trustees: By the Editorial Board, Harry Bakwin, Stewart H. Clifford, and Waldo E. Nelson.

The business address of the Foundation is 3207 Washington Blvd., St. Louis 3, Mo.

Professor Niilo Hallman, chief-of-service at the Children's Hospital, Helsinki, Finland, has accepted the invitation of the Foundation to visit the United States for a month in the early Fall of this year. He will be the Visiting Lecturer for a week at clinics in four different cities. The Trustees are working on the selection of additional clinics to which pediatricians from Canada and the United States will be invited as Lecturers.

THE T & A ENIGMA

IF the question were asked as to the value of the T & A operation, most pediatricians would reply that they had seen it help some children greatly, but that its widespread and indiscriminate use was regrettable. They would say, further, that it was only indicated in children who were carefully selected and who had been under observation for some time. The older men would probably add they were glad the days were over when the operation was almost a routine procedure and parents were led to believe that every child must have the tonsils out.

It is just here, as Bakwin points out in this issue (page 339), that they would be wrong. Herein lies the "enigma." His figures show that, despite the many studies pointing out the uselessness of indiscriminate tonsillectomy and the dangers associated with the operation, it is still an extensively and unnecessarily used procedure.

Where does the fault lie that leads to such "bad practice" continuing is the important question. Is it perhaps that the pediatric staffs in our medical schools are so interested in and occupied with the rare and esoteric that they are not interested in and are bored by the plebeian ailments of children, and thus the sound teaching that the practioner needs is neglected? It is rather shocking to find that the studies reporting on the uselessness of and the dangers associated with the T & A operation have had so little effect.

HYPOGLYCEMIC CONVULSIONS AND THE ALLERGIST

FORBES[1] has pointed out that galactosemia, a metabolic disease resulting from a congenital inability to metabolize galactose, may in early infancy be confused with allergy to cow's milk and must at times be considered in the differential diagnosis of such allergy. The first communication concerning this in medical literature other than the original observation of Forbes appeared recently by Wilhelm.[2]

The purpose of this communication is to direct the attention of those interested in allergy to another metabolic disease, even less common than galactosemia, which should be borne in mind if convulsions due to allergy to cow's milk are suspected in early infancy. Cochrane and associates[3] described for the first time convulsions in infants secondary to hypoglycemia sometimes of familial origin precipitated by the feeding of an amino acid in excess of a critical amount. The circumstances of these cases were such that a pediatrician familiar with the fact that convulsions might, on some occasions, result from allergy to foods would probably have suspected that as the cause. This is especially true since ACTH and cortisone are said to exert a favorable effect in some of these infants.

Cochrane and associates described three infants, two of them sisters, hospitalized at the ages of 2½ months and 4 months, respectively, because of convulsions which occurred after cow's milk feedings had been substituted for breast milk. Allergy must have been suspected in the second of these infants because a soybean milk was tried, but the convulsions persisted. A biopsy of the pancreas in the first case showed only some edema. A third child was hospitalized at 5 months because of convulsions which took place under the same circumstances. Biopsy of a resected portion of the pancreas showed about four times as many islets as normal. Glucose tolerance tests in all three cases were normal. In the first two, the father had a history which was compatible with that of hypoglycemic convulsions, and in the third a maternal uncle had "fits" of undetermined origin. Two unrelated infants with this condition, one familial and one not, are now under study at Genesee Hospital.[4]

While these infants would fall into the general group of spontaneously occurring hypoglycemia described by McQuarrie,[5] in these particular infants it was discovered that the amino acid, leucine, produced marked hypoglycemia resulting in convulsions. Breast milk contains 161 mg. per cent of leucine, cow's milk contains 356 mg. per cent, and one of the popular soybean milks used in this country contains 220 mg. per cent.[6] For purposes of diagnosis, a casein test meal or a leucine test meal may be used although the latter is much more palatable and probably more accurate. In Cochrane's studies, casein was used in the proportion of 1.5 Gm. per kilogram of body weight and leucine 0.15 Gm. per kilogram body weight (equal to the amount of leucine contained in the standard test dose of casein). I would like to suggest that should the infant begin to show evidence of convulsing on such a test meal, this tendency could be quickly corrected by the intramuscular injection of 10 per cent dextrose,[7] although oral administration should be adequate if it is started early enough and the infant is able to swallow.

J. G.

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THE ACID-BASE STATUS OF HUMAN INFANTS IN RELATION TO BIRTH ASPHYXIA AND THE ONSET OF RESPIRATION

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EARLIER studies[1] have led to the conclusion that respiratory failure in the newborn is due to anoxia. The aim of the present study has been to evaluate the birth status of the infant and to time the onset of respiration in relation not only to the arterial oxygen saturation but also to the carbon dioxide tension (Pco_2), the pH, and the total available buffer. Although the pH and pCO_2 have been measured previously,[2-5] they have not been considered as reflecting the duration of an episode of asphyxia. The term "asphyxia," as defined by Schmidt,[6] has been adopted since it *denotes a simultaneous decrease both in the intake of oxygen and the elimination of carbon dioxide*, i.e., anoxia plus hypercapnea. The way in which hypoventilation or asphyxia changes these variables, producing first a respiratory acidosis followed by a superimposed metabolic acidosis,[6-11] has been extensively reported in animals and adults.

MATERIAL AND METHODS

Blood samples were obtained from the artery and vein in a clamped segment of the umbilical cord at the moment of delivery. The samples were collected in greased syringes, the dead spaces of which were filled with a concentrated heparin solution.

Analysis of the samples for oxygen, carbon dioxide, oxygen capacity,[12] pH,[13] and hematocrit[14] was performed as soon after collection as possible, usually within 2 hours, the samples being rotated in iced water. The majority of oxygen saturations were measured by a manometric method.[12] Several bloods were analyzed with the double scale cuvette oximeter[15] or by the method of Nahas using the Beckman spectrophotometer.[16] All three methods were standardized against the manometric analysis of Van Slyke.[17] The microgas analysis was found to vary by ± 1 per cent[12] while

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the standard deviation of the differences was for the Beckman ± 1.3 per cent over the entire range, and for the cuvette oximeter ± 2 per cent over 40 per cent saturation and ± 3.5 per cent below 40 per cent.

The P_{CO_2} and buffer base (BB) were calculated from the Singer and Hastings nomogram[67] using the pH, the CO_2 content, and the hematocrit. The term "buffer base" refers to the total available buffer and includes both the bicarbonate (or alkali reserve), the protein, and the hemoglobin. In the study of metabolic acidosis, it is a more valuable measurement than the bicarbonate alone.

The recent work of Dawes and associates,[18] on the fetal circulation, indicates that the umbilical artery blood represents the blood going to the fetal tissues and not fetal venous blood. Contrary to earlier studies by Barcroft and his associates[19, 20] and Huggett,[21] the blood supplying the brain contains only slightly more oxygen than that in the umbilical artery (Fig. 1).[22] The more accurate interrelationship of the oxygen saturations in the various vessels was obtained by withdrawing blood from eight major vessels simultaneously rather than using discrete samples collected over a period of time. Since the cineangiographic evidence of Lind and Wegelius[23] suggests that the fetal circulation in the human being resembles that in the lamb, the umbilical artery has been taken to represent the blood supplying the tissues of the infant at the moment of delivery.

One minute after the complete birth of the infant, he was evaluated and given a score.[24] Two points were given for each of the following: color, respiration, muscular tone, nasal irritability, and heart rate. All the infants with a score of 8, 9, or 10 are vigorous and have breathed within seconds of delivery. In this group, scores less than 10 have reflected a lower score for color. The infants with a score of 4 or less are blue and limp and have failed to establish respiration by one minute. With increasing depression the last two vital signs, reflex irritability and heart beat, disappear, in that order.

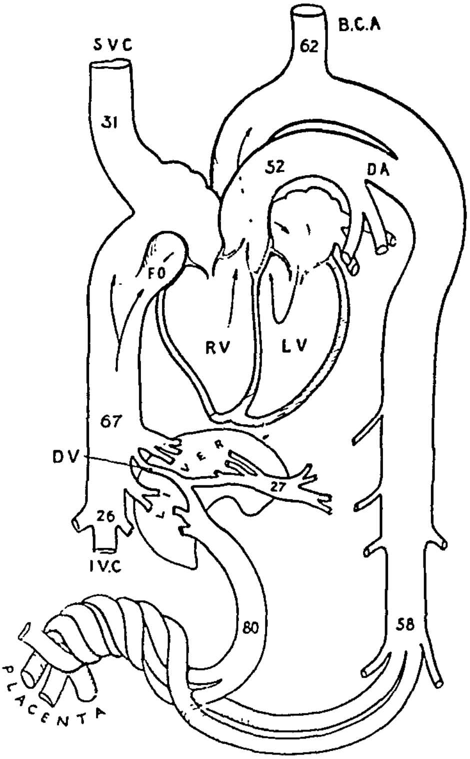

Fig. 1.—Diagram of the fetal circulation. The figures indicate the percentage oxygen saturation of blood withdrawn simultaneously from various vessels, and averaged from determinations on 6 lambs. I.V.C., inferior vena cava; S.V.C., superior vena cava; D.V., ductus venosus; F.O., foramen ovale; D.A., ductus [illegible] brachiocephalic artery. [illegible] the Heart and Lungs a[illegible] Harbor Symposia on Quantitative Biology, Vol. XIX, 1954.)

The time required for the infant to establish spontaneous and continuous respirations is termed, "time to sustained respiration." (T.S.R.)

To determine the biochemical status of the depressed group, samples from either the umbilical artery, the portal vein area in the liver, or from the right or left atria have been used. This has been considered justifiable for several reasons. In many of these infants the heart rate is slow and the pulse feeble. The blood pressure has not yet been measured at this time, but from the response of infants 2 to 11 days old[25] and from that of newborn and fetal lambs[26] to severe anoxia, it is likely to be low. Therefore, the cord circulation will be poor, especially if there is compression. Frequently, the cord is collapsed and bloodless or the blood is present in loculated sections between areas of complete occlusion. In such cases, a sample of the circulating blood from the infant, either arterial or venous, if obtained before the onset of respiration, will give a more reliable indication of his condition. All the portal vein samples were obtained during resuscitation (artificial expansion of the lungs under positive pressure) about the time the first spontaneous breath was taken. Consequently, the oxygen level will be higher, the P_{CO_2} somewhat lower, and the pH higher than prior to the resuscitation. However, the BB, which returns to normal relatively slowly, may be expected to indicate more accurately the severity of the asphyxia.

RESULTS

The biochemical analyses of the umbilical cord blood of 101 babies are presented in Table I and Figs. 2 and 3. The data have been arranged according to the type of delivery (vaginal or section) and the Apgar score of the infant at one minute.

There is a wide range in the oxygen levels in both the umbilical artery and vein blood and in the A-V difference. All the infants exhibited some degree of asphyxia with a low oxygen saturation and a high CO_2 tension. Of the 63 umbilical artery samples, 26 had an oxygen saturation below 10 per cent and 7 had no measurable oxygen. Fourteen of these severely anoxic infants were not depressed (score 8 and 9) and cried spontaneously within seconds of delivery (Fig. 2). Four were in the intermediate group (score 5 to 7) and 8 were in the depressed group (score 0 to 4). The highest umbilical artery oxygen saturation recorded was 51 per cent.

The umbilical artery pH ranged from 7.00 to 7.35, with a mean of 7.26 for the vigorous and 7.14 for the depressed infants. The P_{CO_2} ranged from 39 to 98 mm. Hg, with a mean of 55 for the vigorous and 74 for the depressed infants, indicating a respiratory acidosis.

A depression of the BB below the normal of 42 mEq./L. for pregnant women (normal for adult males 47 to 50) revealed the presence of a superimposed metabolic acidosis in a number of instances (Fig. 3).

A comparison has been made between the pH, and P_{CO_2}, and BB in either portal vein or umbilical artery blood in the depressed infant and umbilical artery samples from the vigorous group (Table II). Both the pH and BB are significantly lower while the P_{CO_2} is significantly higher in the depressed infants $p < .01$. The severe degrees of metabolic acidosis

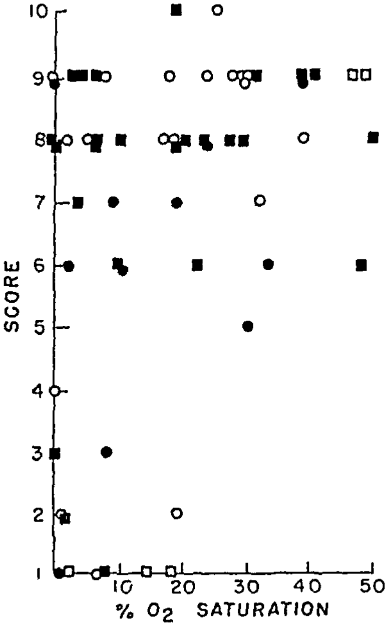

Fig. 2.

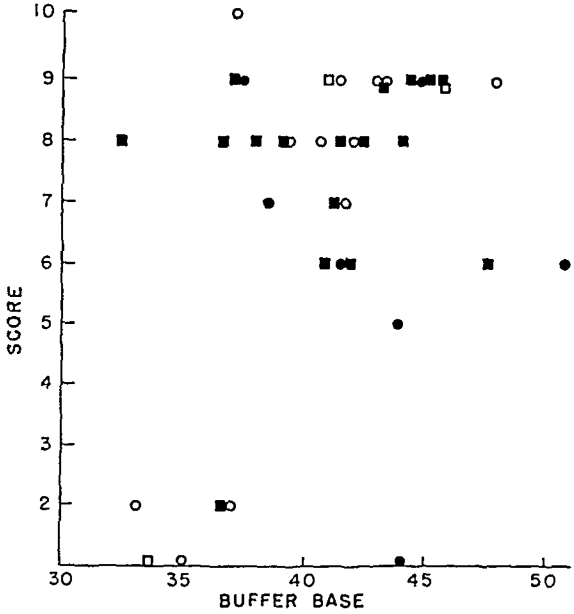

Fig. 3.

Figs. 2 and 3.—○ Vaginal delivery—regional anesthesia; ● Vaginal delivery—inhalation anesthesia; ■ Cesarean section—regional anesthesia; □ Cesarean section—inhalation anesthesia.

Fig. 2.—Umbilical artery—oxygen saturation. Comparison of clinical status of infant at birth with arterial oxygenation.

Fig. 3.—Umbilical artery—buffer base. Comparison of clinical status of infants at birth with arterial buffer base.

TABLE I. BIOCHEMICAL FINDINGS IN THE UMBILICAL ARTERY AND VEIN

			OXYGEN % SAT.		PH		P_{CO_2} MM. HG		BB MEQ./L.		
NO.	NAME	SCORE	ARTERY	VEIN	A	V	A	V	A	V	ANESTHESIA AND COMPLICATIONS
		8-10		*Regional Anesthesia*				*Vaginal Delivery*			
1	Lo	9	0	24	7.32	7.42	45	39	41	46	None
2	Mo	8	2	29	7.19	7.27	62	50	39	41	Spinal
3	Bur	8	6	68	-	7.20	-	45	-	37	None
4	Vel	8	7	67	-	-	-	-	-	-	Caudal
5	Sc	9	9	-	7.26	-	59	-	43	-	Pudendal
6	Irv	9	-	30	-	-	-	-	-	-	Saddle
7	Thos	10	-	45	-	7.24	-	39	-	42	Pudendal
8	Pier	8	17	59	7.20	7.28	63	49	41	42	Pudendal
9	Bal	9	19	48	-	7.40	-	42	-	47	Spinal
10	Me	8	19	64	-	7.27	-	40	-	37	Epidural
11	Yo	9	25	34	-	-	-	-	-	-	None
12	Sant	9	28	-	7.31	-	48	-	43	-	Pudendal
13	Rod	9	30	-	7.37	-	47	-	48	-	Spinal
14	Jack	9	30	65	7.27	7.32	-	40	-	41	Pudendal
15	Jo	9	30	-	7.33	-	48	-	45	-	Caudal
16	Ha	10	31	61	7.15	7.20	64	49	37	37	Caudal
17	Wo	8	45	72	-	7.36	-	35	-	42	Caudal
Average			19.8	47.6	7.26	7.29	54.5	42.8	42.1	41.2	
								Cesarean Section			
18	Jo	8	0	72	-	-	-	-	-	-	Spinal
19	Do	8	0	23	-	-	-	-	-	-	Spinal
20	Hi	9	3	15	-	-	-	-	-	-	Spinal
21	Ro	9	5	12	7.30	7.41	50	36	43	45	Spinal
22	Ca	9	6	9	-	7.17	-	69	-	39	Spinal
23	Sch	9	7	29	7.10	7.22	64	46	37	38	Spinal
24	Lev	8	7	10	-	-	-	-	-	-	Spinal
25	Tr	8	11	23	7.10	7.12	77	69	36	36	Spinal
26	Mi	10	19	72	-	-	-	-	-	-	Spinal
27	Rod	8	19	30	7.14	7.19	81	70	38	39	Spinal
28	Sh	8	-	13	-	7.24	-	63	-	43	Spinal
29	Fo	9	-	40	-	7.26	-	50	-	41	Spinal
30	Ri	8	-	41	-	7.20	-	57	-	39	Spinal
31	Ha	10	-	72	-	7.20	-	51	-	39	Spinal
32	Mag	8	21	44	7.22	7.29	54	43	39	40	Spinal
33	Lo	8	24	53	7.27	7.31	53	41	42	41	Spinal
34	Sc	9	-	31	-	-	-	-	-	-	Spinal
35	Bur	8	28	67	7.27	7.29	50	43	41	41	Spinal
36	Ri	8	30	32	7.04	7.17	74	51	32	35	Spinal
37	Pr	9	32	65	7.33	7.35	51	44	45	45	Spinal
38	Reu	9	32	51	7.26	7.29	59	51	44	43	Spinal
39	Men	9	39	70	7.30	7.36	54	45	45	45	Spinal
40	Ra	9	41	62	-	-	-	-	-	-	Spinal
41	O'R	8	51	79	7.33	7.37	45	37	44	45	Spinal
Average			19.7	42.3	7.22	7.26	59.3	50.9	40.5	40.8	
				Inhalation Anesthesia				*Vaginal Delivery*			
42	Rei	9	0	34	7.33	7.37	59	45	37	39	Cyclopropane
43	Rad	8	25	67	7.26	7.33	-	-	-	-	Cyclopropane
44	Da	9	39	65	-	7.28	-	47	-	41	Cyclopropane
45	Go	8	-	-	7.25	7.25	49	47	42	41	Cyclopropane
46	Li	8	-	44	-	-	-	-	-	-	Cyclopropane
47	New	8	-	47	-	-	-	-	-	-	Cyclopropane
48	Deigh	10	-	62	-	7.31	-	46	-	-	Cyclopropane
49	May	8	-	63	-	7.30	-	46	-	-	Cyclopropane
50	Kr	8	-	68	-	-	-	-	-	-	Cyclopropane
51	Ga	9	-	69	-	7.46	-	-	-	-	Cyclopropane
52	Meu	8	-	68	-	-	-	-	-	-	Cyclopropane
53	Ro	9	-	75	-	7.33	-	49	-	-	Cyclopropane
54	Mo	9	-	79	-	7.46	-	32	-	47	Cyclopropane
Average			21.3	61.7	7.28	7.35	54	44.5	39.5	42.0	

TABLE I—CONT'D

NO.	NAME	SCORE	OXYGEN % SAT.		pH		P_{CO_2} MM. HG		BB MEQ./L.		ANESTHESIA AND COMPLICATIONS
			ARTERY	VEIN	A	V	A	V	A	V	
								Cesarean Section			
55	Ch	9	48	78	7.27	7.31	49	42	41	42	Cyclopropane
56	Ru	9	49	85	7.30	7.35	52	48	45	46	Cyclopropane
Average			48.3	81.5	7.28	7.33	50.5	44.9	43.2	43.9	
				Inhalation Anesthesia				*Vaginal Delivery*			
57	To	8	9	29	7.28	7.33	46	40	41	42	N_2O
58	Br	8	-	26	-	-	-	-	-	-	N_2O
59	Ha	8	18	30	7.20	7.26	-	-	-	-	N_2O
60	Va	9	-	45	-	7.33	-	50	-	46	N_2O
61	Camp	8	23	-	7.33	-	51	-	47	-	N_2O
62	Men	9	44	-	7.40	-	39	-	46	-	N_2O
63	Pier	8	-	81	-	7.29	-	-	-	47	N_2O
Average			23.5	42.2	7.30	7.30	45.3	45	44.6	45.0	
		5-7		*Regional Anesthesia*				*Vaginal Delivery*			
64	Dur	6	-	35	-	7.25	-	55	-	42	Pudendal
65	Mil	7	33	56	7.36	7.45	39	32	42	44	Caudal
66	DeJ	6	-	57	-	7.28	-	48	-	-	Caudal
67	Ray	5	-	61	-	7.37	-	43	-	-	Caudal
Average			33	52.2	7.36	7.33	39	44.5	42	43	
								Cesarean Section			
68	Beau	7	4	31	7.21	7.33	67	45	41	43	Spinal
69	Aiel	6	10	32	7.22	7.33	64	43	42	42	Spinal
70	Beas	6	23	30	7.16	7.23	69	57	41	41	Spinal
71	Ortiz	6	48	84	7.39	7.39	44	40	47	47	Spinal
72	Ja	5	-	83	-	-	-	-	-	-	Sample before delivery
Average			21.2	52.0	7.24	7.32	61.0	46.2	42.7	43.2	
				Inhalation Anesthesia				*Vaginal Delivery*			
73	Gai	6	2	40	7.21	7.24	69	55	42	41	Cyclopropane
74	Mel	7	9	42	7.23	7.22	53	46	38	37	Cyclopropane
75	Gib	6	11	48	7.22	7.29	92	54	51	46	Cyclopropane
76	Val	7	19	37	7.25	7.28	-	-	-	-	Cyclopropane
77	Riv	5	30	47	7.23	7.26	67	56	44	44	Cyclopropane
78	Rei	7	-	49	-	-	-	-	-	-	Cyclopropane
79	Ley	7	-	54	-	7.36	-	39	-	43	Cyclopropane
80	Len	5	-	72	-	-	-	-	-	-	Cyclopropane
81	Kel	6	34	73	7.27	7.32	-	-	-	-	Cyclopropane
Average			17.5	51.3	7.23	7.28	70.2	50.0	43.7	42.2	
				Inhalation Anesthesia				*Cesarean Section*			
82	Pi	5	4	11	-	7.35	-	38	-	40	Cyclopropane
								Vaginal Delivery			
83	Pa	7	14	24	7.23	7.23	56	54	43	43	N_2O
		0-4		*Regional Anesthesia*				*Vaginal Delivery*			
84	Gou	4	0	17	-	-	-	-	-	-	Caudal
85	Sua	2	1	9	7.01	7.03	99	93	33	34	Saddle
86	Bu	1	7	-	7.08	-	78	-	35	-	Caudal
87	Wa	1	-	21	-	7.28	-	57	-	43	Pudendal
88	Fried	2	19	34	7.18	7.25	57	46	37	39	4+ nucal cord with facial petechiae; spinal
Average			6.7	20.2	7.09	7.18	78.0	65.3	35.0	38.6	
								Cesarean Section			
89	Per	3	0	10	-	-	-	-	-	-	Spinal
90	Em	2	1	41	7.17	7.20	63	53	38	38	Cord prolapse thru wound for 2 min.
91	Mer	1	7	63	-	-	-	-	-	-	Local and Pentothal
Average			2.6	38.0	7.17	7.20	63	53	38	38	

TABLE I—CONT'D

NO.	NAME	SCORE	OXYGEN % SAT.		pH		Pco_2 MM. HG		BB MEQ./L.		ANESTHESIA AND COMPLICATIONS
			ARTERY	VEIN	A	V	A	V	A	V	
					Inhalation Anesthesia			*Vaginal Delivery*			
92	Ga	1	0	0	7.08	7.07	94	93	34	34	Cyclopropane
93	Ha	1	-	21	-	-	-	-	-	-	Cyclopropane
94	Br	3	15	51	-	7.27	-	61	-	46	Cyclopropane
95	Su	1	18	38	7.00	7.11	-	-	-	-	Ruptured uterus; Cyclopropane
Average			11.0	27.5	7.04	7.15	94	77.5	34	40	
								Cesarean Section			
96	Mul	1	0	62	7.32	7.37	53	40	44	44	Cyclopropane 4+ nucal cord
97	Fent	3	8	27	7.32	7.38	-	-	-	-	Cyclopropane
98	Pier	2	-	29	-	7.33	-	44	-	43	Cyclopropane
Average			4	39.3	7.32	7.36	53	42	44	43.5	
								Vaginal Delivery			
99	Wa	1	-	42	-	7.07	-	71	-	33	Ether
100	Tr	1	-	67	-	7.25	-	49	-	41	Prolapsed cord; ether
101	Mer	3	-	56	-	7.26	-	50	-	41	Chloroform
Average				55		7.19		56.6		38.3	

and derangement of pH and Pco_2 which were observed as a result of prolonged apnea are illustrated in Table III and Fig. 4. Here the portal vein or atrial samples taken at the onset of respiration have been compared with the biochemical status of the cord blood when samples could be obtained. In all instances, the biochemical measurements in the portal vein blood showed a greater degree of asphyxia.

DISCUSSION

These studies have revealed the varying degrees of asphyxia which occur during all forms of delivery. Contrary to earlier reports,[1, 4, 5] an infant may make the initial respiratory gasps with no measurable oxygen in his arterial blood. In this sense, anoxia, as measured by the oxygen saturation of the umbilical artery's blood, correlates poorly with postnatal vigor. The significant difference which has been demonstrated between the vigorous and depressed infants lies in the pH, Pco_2, and BB (Table II). Previous studies have shown that these variables give a measure of an asphyxial insult,[6-11] a brief period of asphyxia causing in the main a respiratory acidosis with a raised Pco^2 and little change in the BB. This pattern of change may be seen in the vigorous infants (score 8-10, Table I). If on the other hand, the asphyxia is prolonged, a marked reduction in the BB occurs (depressed infants score 0-4, Table I), indicating a metabolic acidosis which has become superimposed on the respiratory acidosis.

From this it is evident that the response of the infant to asphyxia is identical to that of the adult.[6-11] The rapid recovery after birth[29] also follows the adult pattern. In the vigorous infants the absence of a severe metabolic acidosis in the presence of a high Pco_2 indicates that the period of asphyxia has been quite brief. In

TABLE II. STATISTICAL COMPARISON OF VIGOROUS AND DEPRESSED INFANTS

	VIGOROUS INFANTS (SCORE 8-10) UMBILICAL ARTERY SAMPLES			DEPRESSED INFANTS (SCORE 0-4) UMBILICAL ARTERY OR PORTAL VEIN			
	NUMBER	MEAN	S.D.	NUMBER	MEAN	S.D.	P
O_2	43	22.2	21.77	12	6.3	7.3	
pH	30	7.26	0.085	10	7.04	0.142	$p < .01$
PCO_2	27	55.3	10.25	9	82.0	19.93	$p < .01$
BB	27	41.5	3.68	10	31.4	6.93	$p < .01$

TABLE III. BABIES SEVERELY DEPRESSED AT BIRTH

			CHANGES IN pH, Pco_2, AND BB WITH TIME				
NAME	SCORE	SITE	OXYGEN % SATURATION	pH	Pco_2	BB	
Fr	2	Umbilical artery	19.2	7.18	57.0	37.0	Spinal anesthesia, cord tightly round neck; facial petechiae; T.S.R.,* 3 min., 35 sec.
		Portal vein	21.2	6.98	90.2	30.5	P.V. sample 25 sec. after first spontaneous respiration
Fc	3 ↓	Umbilical artery	8.0	7.32			Anesthesia cyclopropane; thick meconium-stained mucus in pharynx
at 3 min.	1	Portal vein	50.9	7.10	77.0	37.8	T.S.R., 12 min.; P.V. sample 2 min. after first spontaneous respiration
Wa A Twins	1	Umbilical vein	41.9	7.06	70.5	33.2	Anesthesia chloroform; twins locked, 2 weeks premature; T.S.R., 25 min.
A		Portal vein	61.9	6.91	69.5	24.1	P.V. sample 2 min. after first spontaneous respiration
B	1	Portal vein	55.9	6.80	114.5	21.7	P.V. sample 1 min. after first spontaneous respiration
Ch	0	Left atrium	93.0	6.74	39.9	<15.0	Emergency section for prolapsed cord; no heartbeat at birth. cardiac massage Sample after 25 min. of artificial ventilation when infant took first spontaneous gasp

*T.S.R. = time from birth to spontaneous respiration.

light of this, earlier interpretations that the fetus is normally adjusted to these high tensions of carbon dioxide[27] can no longer be accepted.

The high score group of infants, those who were well oxygenated, had little or no depresion of the BB. Where the oxygen saturation was 10 per cent or less in this group, in all but one case the BB value was slightly below the average for the group but well above the average for the depressed infants. The low BB values occasionally seen in this group were associated in most instances with a second stage of labor of 2 hours or more or slowing and irregularity of the fetal heart during the first stage of labor. This undoubtedly reflects anoxia during labor which is sufficient to disturb metabolism but not enough to depress the infant significantly.

Several factors probably contribute to the asphyxia which appears to occur as a normal phenomenon in almost every delivery.

Cord Compression.—

Any reduction in the blood flow through the cord will lower the arterial oxygenation since the fetal venous blood (26 to 31 per cent saturated in the lamb[22]) will be passing directly into the arterial circulation with little or no mixing with oxygenated blood from the placenta. The saturation in the umbilical vein will remain unchanged[30] or may even be raised, since the fetal blood will remain in contact with the blood in the intervillous space for a longer period; but with reduction in flow, this blood does not reach the fetal circulation. The reduction in flow can be caused by kinking, prolapse, pressure between the fetus and the rim of the pelvis or vagina, or when the cord is wound tightly round the neck. Clemetson and Churchman[31] have shown the large difference in saturation between the umbilical artery blood and that in the vein, which may be found in this last situation. Manipulation of the cord causes constriction of the umbilical arteries, which in turn slows the stream of blood through the placenta. Barcroft[30] has vividly described the acute sensitivity of these vessels, particularly at term.

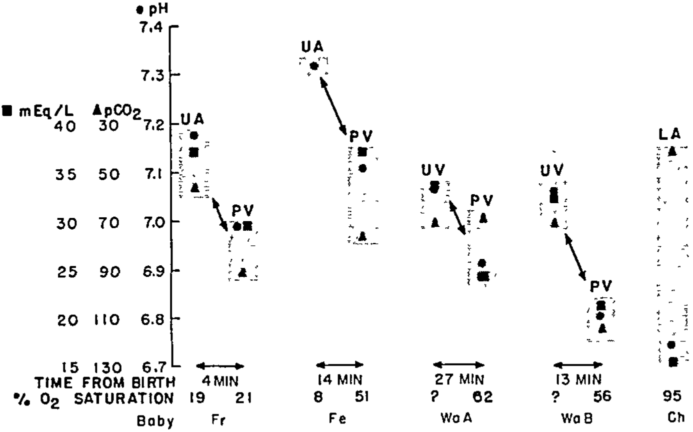

Fig. 1.—Changes in pH, pCO₂, and buffer base in 5 depressed newborn infants. UA—umbilical artery; UV—umbilical vein; PV—portal vein; LA—left atrium. The same umbilical vein sample has been used for comparison in twins Wa A and Wa B

The values for Ch represent pure metabolic acidosis remaining after 25 minutes of resuscitation. The oxygen saturation in the LA was 99 per cent.

Changes in Uterine Blood Flow.—

a. *Posture:* The supine position has been shown to be associated with compresion of the mother's inferior vena cava by the heavy gravid uterus. Howard and his associates[32] have demonstrated that the pressure in the femoral vein may be raised from 108 to 239 mm. H_2O by this mechanism. This rise will decrease the pressure gradient between the uterine artery and vein and will tend to reduce blood flow through the uterus. When the obstruction to the inferior vena cava is more complete, sufficient to cause hypotension in the mother,[33] an even greater reduction in flow will occur. This factor must be considered in cesarean section during which the mother may be flat on her back for 15 or 20 minutes before the baby is delivered. It is probable that the occasional very low oxygen value obtained in both cord vessels at cesarean section under local anesthesia is caused partly by this obstruction effect[34] (Table I).

b. *Hypotension with spinal anesthesia or maternal hemorrhage:* Hypotension not infrequently produced by spinal anesthesia will reduce the pressure gradient and the uterine flow. Fetal distress revealed by excessive movements or slowing of the fetal heart occurs under such conditions. Whether because of hypotension, increased uterine tonus, or some other factor as yet undetermined, the oxygen saturation in lambs delivered under spinal anesthesia is uniformly lower than in those delivered under pentobarbital.[35] Henderson reports a similar finding in human beings in comparing spinal and inhalation anesthesia.[36] Hypotension as a result of hemorrhage is likely to have an even more profound effect on reducing the uterine flow.

c. *Uterine contraction:* Caldeyro-Barcia[37] has shown that with a strong uterine contraction, blood flow through the uterus and placenta is completely arrested.

Uterine vein samples withdrawn a short time before delivery of the fetus by cesarean section[38] show, in most instances, a higher oxygen saturation than does umbilical vein blood obtained after delivery from a clamped segment of cord. This is contrary to the figures which Barron and Meschia[39] give in studies on the placental exchange of respiratory gases in the sheep and rabbit, and suggest that in the few minutes between the sampling from the uterine vein and delivery of the infant a reduction in oxygen transfer has occurred. Changes in the uterine circulation with manipulation, incision, and the immediate contraction which occurs as the amniotic fluid gushes out could account for this difference.

d. *Partial separation of the placenta:*

This will reduce the effective area of diffusion and will lead to a lower oxygenation of the fetus.

Reduction in the Maternal Exchange of Respiratory Gases.—

a. *Breath holding and straining:* Both of these occur during vaginal delivery, when anesthesia is not given or is minimal, and may result in a significant lowering of the maternal arterial oxygen saturation.

b. *Inhalation anesthesia:* The effect of inhalation anesthesia upon fetal oxygenation varies as much with the agent being used as with the clinic reporting the study. Good and poor results have been claimed for all agents. Because of a variety of techniques and the many additional factors noted above, it is difficult to determine the effect of the agent itself. However, if the mother has any airway obstruction during anesthesia, her CO_2 elimination and oxygen uptake will be impaired. This effect will be reflected in the fetus if delivery is prolonged.

It has been assumed by some authors that samples obtained at cesarean section under regional anesthesia represent normal in utero conditions in the human being.[28] This has led to the concept of "Everest in utero" and to the belief that, with placental aging, fetal arterial oxygen saturation falls as term approaches.[40, 41] However, any sample obtained either at vaginal delivery or cesarean section is unlikely to represent the normal conditions before labor or operation since both uterine blood flow and cord compression cannot be controlled. The multiple factors enumerated above, acting separately or in combination, will all tend to lower the oxygenation of the fetus at delivery. While cord compression will increase the difference in saturation between the umbilical artery and vein, all the other factors will tend to lower the oxygenation of both vessels since they interfere with the exchange between mother and fetus. Undoubtedly, this accounts for the low average but the very wide range in published figures (10 to 60 per cent saturation in the umbilical artery and 10 to 84 per cent saturation in the umbilical vein[3-7, 28, 31, 34, 40-47] [Table IV]). The highest human figures reported are almost identical with the normal value which Dawes and associates[15] and Barron and Meschia[39] observed for lambs. These high values, rather than the average, probably give a truer indication of the normal in utero environment. Further indirect evidence which supports a high intrauterine oxygen environment is found in the color photographs of the unborn human infant taken by means of hysterophotography.[48] Here the infant actually appears to be pink.

TABLE IV. COMPARISON OF OXYGEN SATURATION IN UMBILICAL CORD VESSELS

AUTHOR	AVERAGE PER CENT OXYGEN SATURATION		NUMBER OF CASES		RANGE		DELIVERY
	ARTERY	VEIN	ARTERY	VEIN	ARTERY	VEIN	
Eastman[28]	16	50	15	15	6-27	38-58	Vaginal vertex
	30	63	1	1			Caesarean section
Smith[42]	16	51	37	40	2-48	16-81	
Clemetson &							Vaginal vertex
Churchman[31]	31	63	10	12	2-50	35-84	Spontaneous vaginal vertex
Walker[41]	20	48	9	10	1-28	13-60	Spontaneous vaginal vertex
Rooth & Sjostedt[34]	32	61	69	98	0-62	9-83	Spontaneous vaginal vertex
Present authors (See Table I)	22	49	43	55	0-51	9-85	Cesarean section and vaginal vertex; all vigorous at birth

An interesting advance has been the development of techniques for sampling intervillous blood in human beings during labor.[49] Prystowsky[49] has observed a low oxygen tension in the intervillous space and a marked reduction in the maternal-fetal oxygen tension gradient when the infant proved to be in poor condition at birth. The maternal samples were taken just prior to delivery. While the range of oxygen tension in the intervillous sample was wide in the normal group (72 to 26 mm. Hg), in all but three instances, the individual tensions were considerably below a value which would be compatible with an umbilical vein oxygen saturation of 80 per cent. Such findings indicate that, when the head is on the perineum prior to delivery, the various maternal factors tending to lower the fetal oxygenation may already be in action.

Table III and Fig. 4, showing the differences between the cord blood samples and those obtained from the portal vein, indicate that anoxia causes rapid changes in the pH, P_{CO_2}, and BB. The speed of change as recorded here may be misleading since there was severe cord compression in one infant and one umbilical vein sample has been compared to the two portal vein samples in the case of the twins. However, the rapidity of these changes is well documented in studies on both dogs[8, 9] and adult man.[50] Where the residual air in the lungs has not been washed out with oxygen, the saturation falls to zero in 3 minutes (dogs) and to 28 per cent in 2 minutes (adult man).

The results of the present study emphasize the need for obtaining a sample from within the depressed infant if the limits of respiratory and metabolic acidosis are to be revealed. It is quite possible that these levels may be dangerous enough to cause irreversible cellular damage in the newborn human. If they occur as rapidly as this study suggests and are dangerous, the need for the greatest dispatch in resuscitating an infant with no oxygen reserves is apparent.

Asphyxia in Relation to the Onset of Respiration.—

In vitro and in vivo studies demonstrate that the brain is depressed by oxygen lack,[51, 52] even slight lowering of the oxygen tension depressing the respiratory center.[53] However, through the action of the chemoreceptors which are stimulated by anoxia and continue to function when the oxygen tension has fallen to zero,[6] this depression may be almost completely masked. Under severe anoxia, breathing takes the form of gasps in which the accessory muscles play a major role. The first gasps of the newborn infant are of this type but are soon replaced by quiet and relatively regular diaphragmatic and intercostal breathing following the rapid expansion of the lungs and oxygenation which normally occur within minutes of delivery.[54-56] Although Miller and Behrle[57] have suggested that the chemoreceptor response is poor in the first 24 hours of life, the occurrence of vigorous first breaths under extreme anoxia provides indirect evidence that the chemoreceptors are indeed functioning actively at birth. It is possible that they may be functioning at a higher threshold which was not reached during the induced hypoxia studies of Miller. The direct recording of action potentials from the proximally severed sinus nerve in newborn and fetal animals by Cross and Malcolm[58] is further evidence of activity.

As in the adult, the respiratory center of the infant is acutely sensitive to carbon dioxide[59, 60] and is probably stimulated both directly[61] and indirectly[6] when the P_{CO_2} rises. The high P_{CO_2} shown in most vigorous newborns is likely to play a major role in the first gasp if the anoxia is not severe. Finally the low pH, acting through the chemoreceptors,[6] and the flood of sensory impulses crowding in from the skin, the muscles and the joints[62] doubtless constitute important stimuli of the first breaths. These will be augmented by stimuli from the rapidly adapting stretch receptors in the alveoli[63] as the lungs expand.

With progressively severe asphyxia, a point is reached when the respiratory center is finally so depressed that it is unable to respond.[51] The P_{CO_2} and pH which previously stimulated the cells now act as depressants. Schmidt has termed this the Reversal. The exact levels of P_{CO_2} or pH which will depress the center appear to vary depending on the oxygen level, the degree of metabolic acidosis, and the presence or absence of narcotic drugs.[63-65] As for adults, the multiple factor theory of Gray[66] is the most acceptable to interpret the response of the infant respiratory center. All four factors must be considered in each individual case.

Although the infant may take his first breath when there is no measurable oxygen in umbilical artery blood, the presence of oxygen appears to be essential if respiration is to occur in the presence of severe respiratory and metabolic acidosis. This is apparent not only in the vigorous infants (Table I) who have a particularly high P_{CO_2} or low BB but also in the depressed group. In the latter, spontaneous respiration occurred only after artificial oxygenation of the infant.

When anesthetic or narcotic agents are present in significant amounts, spontaneous respiration is seen only when the asphyxia is mild (Cyclopropane cases, score 8-10, Table I). With high dosage, when drugs are almost wholly responsible for the apnea, the infant frequently makes his first gasp after an interval of 1 to 2 minutes probably as a result of the stimuli arising as the asphyxia increases (infants receiving cyclopropane, score 5-7). These are the infants who appear vigorous, with good tone and heart rate, yet fail to breathe immediately. In other instances in which asphyxia is already severe, a small dose of anesthetic or narcotic will appear to cause profound depression.

SUMMARY AND CONCLUSIONS

1. Some degree of asphyxia, usually of brief duration, occurs as a result of the delivery process and is a normal finding in all births. This may be caused by several factors operating on the fetal and maternal circulations at the time of delivery. Because of these factors, the cord blood obtained following delivery of the infant can rarely, if ever, give a true indication of the normal intrauterine environment.

2. The blood in the umbilical artery represents the blood supplying the fetal tissues, the blood which reaches the head and upper extremities containing on the average only 4 per cent more oxygen. The blood in the umbilical vein will be related more to the placental exchange at or just prior to delivery and may bear little relation to the fetal arterial oxygen level.

3. Vigorous respiration can occur spontaneously in the absence of measurable oxygen in the umbilical artery blood.

4. Asphyxia produces the same biochemical changes in the infant as in the adult—a respiratory acidosis followed by a superimposed metabolic acidosis.

5. The effects of asphyxia, if not too prolonged, acting through the chemoreceptors, are probably responsible for the initial gasps of the infant.

6. Failure to breathe at birth is caused by either depressant drugs or the severity of the respiratory and metabolic acidosis, the result of prolonged asphyxia.

7. The pH, Pco$_2$, and BB of the newborn infant's blood give a measure of the degree of an anoxic insult. They may change rapidly if he fails to breathe.

8. In evaluating the biochemical status of a depressed infant, a blood sample taken directly from the infant is more representative of his status than is a sample from the umbilical artery.

9. The severe degrees of metabolic and respiratory acidosis seen in depressed infants stress the need for active ventilation and re-oxygenation of these infants immediately after birth.

10. Since inhalation anesthesia administered to the mother will always augment the metabolic depression, regional anesthesia would seem more desirable for delivery of an infant with fetal distress.

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ACID-BASE HOMEOSTASIS OF THE NEWBORN INFANT DURING THE FIRST 24 HOURS OF LIFE

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The low CO_2 content and Pco_2 of the blood of newborn infants, as compared with that of adults, have been frequently reported.[1-6] These findings have been the basis for (1) the concept of a persistent metabolic acidosis,[3,4] (2) a theoretical explanation of the respiratory drive,[5] and (3) speculation concerning the utilization of anaerobic metabolism for energy in the newborn.[3,4] However, the blood of women during the last trimester of pregnancy also shows diminished CO_2 content and Pco_2.[7-15] The cause of this change is not known; it has been attributed to hyperventilation,[13] and to the effect of progesterone.[14] Total plasma base is reduced by 8 mEq./L.,[10] but plasma organic acids are normal[11] or reduced.[10] It is the purpose of this paper to compare the acid-base balance of newborn infants with that of pregnant women and to discuss the possible significance of this relationship.

MATERIALS AND METHODS

Umbilical arterial bloods were collected from clamped segments of umbilical cord and were taken to represent the status of the infant's systemic arterial blood at the end of parturition. The analyses of these bloods have been presented.[16] Left atrial samples were drawn from newborn infants during the first hour after birth or at the third hour and again at approximately 24 hours, during atrial catheterization via the umbilical vein. It was not technically possible to sample all infants serially. All infants were quiet during the procedure, many of them sleeping. All weighed over 2,500 grams and were born vaginally or by cesarean section of nondiabetic, nontoxemic mothers. Only bloods of infants with an Apgar score[17] of 6 or better were reported. All infants received routine nursery care, which included a feeding of glucose water at about 8 hours of age, and formula or breast feeding between 12 and 24 hours.

Maternal arterial blood samples were drawn at the time of secondary cesarean section of mothers who were not in labor. Sections were performed under regional anesthesia. Demerol, 50 mg., and scopolamine, 0.4 mg., was the usual premedication, given an hour before surgery. No bloods are reported of any mother who was hyperventilating or restless, who had received inhalation anesthesia, or whose face had been covered with a mask prior to sampling.

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Bloods were collected anaerobically in greased syringes, the deadspaces of which were filled with a concentrated heparin solution. They were rotated through ice water until analyzed. Oxygen saturation, pH, carbon dioxide content, and hematocrit were determined by methods previously described.[16] The pH of atrial blood specimens was measured at 37° C. and was corrected to deep rectal (6-7 cm.) temperature, according to the formula of Rosenthal.[18] The Pco$_2$ was calculated from the Henderson-Hasselbalch equation, using pK′ and solubility coefficient of CO$_2$ corrected to the infant's body temperature according to the values of Severinghaus and his associates.[19, 20] The Pco$_2$ of the other bloods and the buffer base (BB) was determined from the Singer and Hastings nomogram.[21]

RESULTS

The results of the blood gas analyses are shown in Tables I-V. The mean values for 12 maternal samples (Table I) were pH—7.39; plasma CO$_2$ content—19.96 mEq./L.; Pco$_2$—31.7 mm. Hg; and BB—41.8 mEq./L. of whole blood. Despite our maternal control subjects not having been in a basal state, our value for Pco$_2$ was in good agreement with the alveolar Pco$_2$ tension determinations of other authors, which are tabulated below.

Author	*Pco$_2$, mm. Hg*
Rowe[8]	29.9 and 30.9
Goodland et al.[14]	30 (approximately)
H. and E. Bouterline-Young[15]	30.9
Present study	31.7

Our value for arterial plasma CO$_2$ content was somewhat lower than the venous plasma values of other authors, which are tabulated below.

Author	*Plasma CO$_2$, mEq./L.*
Dennis and King[9]	23.1 (venous)
Oard and Peters[10]	22.1 (venous)
Stander et al.[11]	21.8 (venous)
Muntwyler et al.[12]	22.7 (venous)
Present study	19.96 (arterial)

Our value for pH was within the normal adult range and confirms the findings of Kydd.[22]

The data of Tables II-VI indicate that the infant is subjected to a period of anoxia, CO$_2$ retention, and acidosis during parturition which recede rapidly after birth. At 24 hours of age

TABLE I. ACID-BASE BALANCE OF 12 PREGNANT WOMEN AT TERM
ARTERIAL SAMPLES

	OXYGEN SATURATION (PER CENT)	pH BLOOD	Pco$_2$ MM. HG	CO$_2$ CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Dov	95.1	7.38	35	21.3	42.0
Rod	95.0	7.44	28	19.2	42.2
Jac	96.6	7.37	30	18.0	40.2
Ric	96.4	7.42	31	20.1	42.3
Fol	93.7	7.34	35	19.5	40.2
Han	93.4	7.39	32	19.5	40.8
Burn	95.1	7.31	33	17.3	37.4
Bea	96.5	7.47	33	24.4	47.2
Mag	93.6	7.39	33	20.3	41.3
Burk	97.6	7.42	26	17.4	43.0
Lev	95.0	7.41	30	19.9	42.0
Men	94.0	7.39	35	22.6	43.5
Average	95.17	7.393	31.7	19.96	41.84
S.D.	1.36	0.043	2.8	2.08	2.23

TABLE II. ACID-BASE BALANCE DURING BIRTH OF 21 INFANTS
UMBILICAL ARTERY SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Lob	Vaginal	0.0	7.32	44	20.5	41.5
Tor	Vaginal	9.2	7.28	46	22.3	39.6
Dov	Cesarean	0.0	7.23	64	26.5	41.4
Vel	Vaginal	7.0	7.12	64	21.6	33.7
Aio	Cesarean	8.2	7.22	64	27.0	41.7
Lor	Cesarean	23.9	7.27	53	25.5	42.1
Dod	Cesarean	30.9	7.30	50	25.7	43.0
Cha	Cesarean	47.8	7.26	49	23.8	40.9
Jac	Cesarean	30.1	7.28	—	—	—
Rod	Cesarean	30.9	7.30	43	22.5	44.8
Pie	Vaginal	17.2	7.20	63	26.2	40.5
Hal	Vaginal	30.5	7.15	64	23.7	37.1
Bea	Cesarean	4.0	7.20	67	28.3	41.3
Mag	Cesarean	21.1	7.22	54	23.3	39.3
Sch	Cesarean	7.0	7.10	64	21.4	33.7
Mel	Vaginal	9.4	7.23	53	23.2	38.4
Burk	Cesarean	28.1	7.27	50	24.3	41.2
Men	Cesarean	39.5	7.30	54	28.3	44.8
Mon	Vaginal	2.2	7.20	62	25.6	39.2
Rei	Vaginal	0.0	7.18	59	23.5	37.0
Gib	Vaginal	10.5	7.22	92	38.6	51.7
	Average	17.02	7.231	58.4	25.04	40.65
	S.D.	14.41	0.062	10.5	3.89	3.98

TABLE III. ACID-BASE BALANCE DURING FIRST HOUR OF 10 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Woo	Vaginal	93.8	7.31	37	21.3	42.0
Jac	Cesarean	91.7	7.43	28	20.4	44.8
Ric	Cesarean	88.1	7.22	51	22.8	40.5
Burn	Vaginal	94.9	7.22	48	21.2	40.3
Tho	Vaginal	97.4	7.30	42	21.7	42.8
Hal	Vaginal	93.2	7.26	38	18.6	39.5
Bea	Cesarean	94.0	7.35	41	24.3	46.8
Mag	Cesarean	96.0	7.25	34	16.2	37.5
Mel	Vaginal	94.0	7.29	38	19.5	41.1
Del	Vaginal	95.2	7.41	31	20.2	46.4
	Average	93.83	7.304	38.8	20.62	42.17
	S.D.	2.55	0.023	7.3	2.27	3.39

TABLE IV. ACID-BASE BALANCE AT THIRD HOUR OF 7 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Han	Cesarean	98.0	7.29	46	22.5	41.9
Pie	Vaginal	94.4	7.37	36	22.6	46.3
Wal	Cesarean	95.1	7.35	39	23.4	44.8
Burk	Cesarean	95.1	7.31	39	21.3	42.4
Duc	Vaginal	94.4	7.35	41	22.9	45.2
Per	Vaginal	93.2	7.37	32	19.2	43.8
Fly	Vaginal	92.6	7.35	35	21.2	43.2
	Average	94.69	7.341	38.3	21.87	43.94
	S.D.	1.73	0.030	6.1	1.42	1.58

TABLE V. ACID-BASE BALANCE AT 24 HOURS OF 14 INFANTS
LEFT ATRIAL SAMPLES

	TYPE OF DELIVERY	OXYGEN SATURATION (PER CENT)	pH BLOOD	P_{CO_2} MM. HG	CO_2 CONTENT MEQ./L. PLASMA	BUFFER BASE MEQ./L. BLOOD
Burn	Vaginal	92.2	7.35	37	21.1	42.8
Pie	Vaginal	91.7	7.36	39	23.5	45.3
Tho	Vaginal	93.1	7.37	35	21.4	43.8
Mag	Cesarean	98.0	7.39	35	21.7	43.2
Del	Vaginal	96.6	7.42	31	21.1	46.9
Lop	Vaginal	98.0	7.42	31	20.5	46.5
Sil	Vaginal	92.0	7.40	28	18.2	43.5
Bir	Vaginal	86.4	7.48	30	22.5	46.4
Cro	Vaginal	97.5	7.42	33	21.9	46.5
Reu	Cesarean	86.9	7.49	37	20.5	44.5
Sto	Cesarean	97.2	7.41	33	21.8	44.2
Gav	Cesarean	91.9	7.40	37	24.0	47.6
Fly	Vaginal	91.0	7.40	35	22.7	44.9
Bar	Vaginal	92.2	7.41	29	18.6	40.3
	Average	93.19	7.408	33.6	21.38	44.74
	S.D.	3.85	0.039	3.4	1.63	1.98

TABLE VI. STATISTICAL COMPARISON OF INFANT BLOOD VALUES AT EACH TIME WITH MATERNAL CONTROLS*

	pH	p	P_{CO_2}	p	CO_2 CONTENT	p	BUFFER BASE	p
Birth (Umb. A.)	7.23	$<.01$	58.4	$<.01$	25.04	$<.01$	40.7	$>.10$
During first hour	7.30	$<.01$	38.8	$<.02$	20.62	$>.10$	42.2	$>.50$
At third hour	7.34	$<.01$	38.3	$<.01$	21.87	$<.05$	43.9	$<.05$
At 24 hours	7.41	$>.10$	33.6	$>.10$	21.38	$>.05$	44.7	$<.01$
Maternal	7.39		31.7		19.96		41.8	

*p values less than 0.05 are taken to represent statistically significant differences between maternal and infant values.

there is no statistical difference between the means of maternal and infant pH, P_{CO_2}, and CO_2 content. The newborn child would seem to move toward the level of pH and P_{CO_2} to which he was exposed in utero.

Fig. 1 is a plot of the pH and CO_2 content data taken from Tables I-V, showing the changes which occur through time with respect to our maternal control values and to normal adult values as given by Peters and Van Slyke.[23]

In Fig. 2 the results obtained by Graham and Wilson[5] from heel capillary blood of 24-hour-old infants is presented. In this method, blood is obtained by pricking the heel and collecting the blood under mineral oil. The ensuing crying of the infant and the possible loss of CO_2 into the mineral oil may cause variation from basal arterial values. The results of Marples and Lippard[2] for *venous* blood of 1- to 8-day-old infants are shown in Fig. 3. (Comparable *arterial* blood of these infants could be expected to contain 1.5 to 2 mEq./L. less CO_2, bringing these data even closer to the range of maternal control values.) The results of these laboratories tend to confirm our finding that although newborn infants have a CO_2 deficit with respect to normal adults, no such deficit exists with respect to pregnant women near term.

Buffer base rises steadily from birth to a mean level of 44.7 mEq./L. of whole blood at age 24 hours, a value

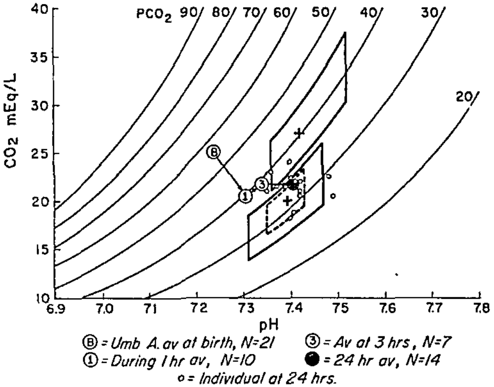

Fig. 1.—The ordinate is mEq./L. plasma CO_2. The abscissa is pH. The curved lines are P_{CO_2} isobars and are logarithmically spaced. The upper quadrilateral represents the range of normal adult arterial values. The lower quadrilateral represents the range of maternal arterial values, with one S.D. from the mean indicated by broken lines.

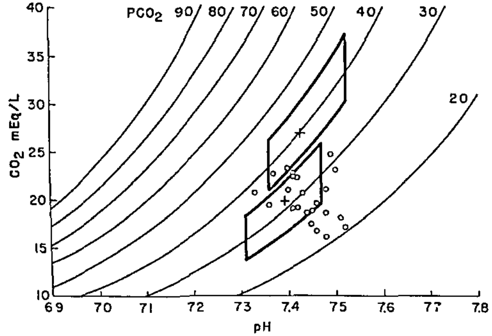

Fig. 2—Capillary (arterial) blood—24 hours of age. Data of Graham and Wilson[5] plotted in open circles. The quadrilaterals represent normal arterial values and data from pregnant women, respectively, as in Fig. 1.

which is higher than the maternal level but lower than the mean normal adult value of 49 mEq./L.[21]

tion and accumulation of intermediary organic acids leading to a metabolic acidosis.

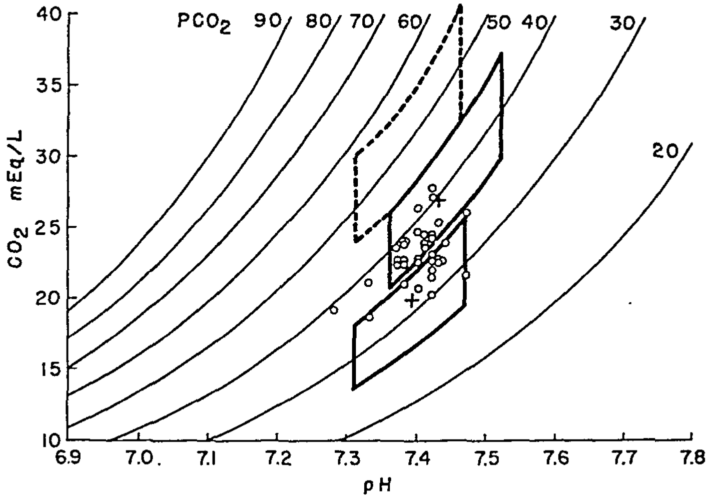

Fig. 3.—Venous blood—ages 1-8 days. Data of Marples and Lippard[3] plotted as open circles. Upper quadrilateral, outlined by dashed lines, includes additional range of adult normal venous blood. Lower quadrilaterals are as for Figs. 1 and 2.

DISCUSSION

From the data of Tables I-VI and Fig. 1, it appears that after the stress of parturition the homeostatic mechanisms of the newborn are directed toward attaining a pH and P_{CO_2} which existed in utero. In reviewing the early work attempting to establish the relation between maternal and fetal CO_2 tension, Barcroft[24] concludes that only a small difference should be expected. Barron,[25] in careful experiments on sheep, has shown that the alkali reserve of the ewe and that of its near-term fetus are almost identical.

Previous attempts to explain the low P_{CO_2} and CO_2 content of the blood of newborn infants dealt chiefly with two hypotheses, as follows: (1) the possibility that hyperventilation due to anoxia caused lowering of P_{CO_2} and (2) the possibility that anaerobic metabolism caused lessened CO_2 production and accumulation of intermediary organic acids leading to a metabolic acidosis.

Hyperventilation Due to Anoxia Hypothesis.—Graham and Wilson[5] have explained the low P_{CO_2} of babies at 24 hours of age as the result of hyperventilation due to anoxic stimulation of the aortic and carotid chemoreceptors. During the first hour of life, they noted oxygen saturation of capillary blood from the heel to the level of 85 per cent, corresponding to an O_2 tension of 50 mm. Hg. They do not state whether the heel was arterialized by warming prior to sampling. Persistent cyanosis of the feet is common in healthy infants during the first day and probably represents local circulatory stasis rather than systemic arterial desaturation. Left atrial saturations during the first day are given in Tables III-V. The saturation is about 94 per cent during the first hour and does not change appreciably with time. These results confirm our suspicion that heel capillary blood may not represent true arterial samples.

We may assume that the respiratory center of the fetus in utero adapts to the low P_{CO_2} environment supplied by its mother and that the rise in P_{CO_2} during parturition supplies one of the chemical drives to respiration, subsequently. It is known in animals that experimental elevation of maternal P_{CO_2} will cause respiratory movements of the fetus in utero.[26]

The exact nature of the hypoxic chemoreceptor drive to respiration in newborn infants is not clear. Cross and Warner[27] have demonstrated a small rise in minute volume during the first week of life in infants exposed to an atmosphere of 15 per cent O_2, while Miller and Behrle[28] have not recorded such a rise in infants, one day old or less, given 12 per cent O_2 (approximate alveolar P_{O_2} of 50 mm. Hg). Thus, the level of arterial P_{O_2} at which Graham and Wilson postulate a strong hypoxic stimulus may not actually produce one. Moreover, the recent work of James and Rowe[29] indicates that very low oxygen tensions cause profound circulatory changes which further decrease systemic arterial saturation. However, both Cross[30] and Miller[31] agree that CO_2 is a potent stimulus to respiration. We postulate that the low P_{CO_2} of the newborn at 24 hours represents the end results of the respiratory center's efforts to attain a level of P_{CO_2} similar to that to which it had been exposed in utero.

Anaerobic Metabolism With Production of Organic Acids and Metabolic Acidosis Hypothesis.—Wilson and his associates[3] postulated that anaerobic metabolism, with diminished CO_2 production, accounted for the low plasma CO_2 content of newborn infants. They cited the prolonged survival time of newborn laboratory animals made severely anoxic as additional proof of the role of anaerobic metabolism in young animals. However, the ability of young laboratory animals to survive anoxic stress is not necessarily proof of increased capacity for anaerobic metabolism over that of the adult. Villee and Kimmelstiel[32] have calculated that anaerobic glycolysis will probably not provide sufficient energy to explain survival in these animals. Moreover, in clinical obstetrics, the infant can withstand only a few minutes of anoxia such as might occur during impaction of the shoulders.

Graham and co-workers[1] have shown the plasma "R" fraction (which consists largely of organic acids) to be 15 mEq./L. for 24-hour-old infants, whereas that of the adult is only 10 mEq./L. Räihä,[33] in discussing fetal tissue metabolism, states, "The acidosis demonstrated in the newborn is largely due to organic acids, chiefly to pyruvic and lactic acids. . . ." The blood pyruvate level he observed was 1.18 mg. per cent or 0.52 mg. per cent above adult levels. Gonzales and Gardner[34] have shown a similar difference in pyruvate level between infants during the first 24 hours of life and pregnant women. Such a difference would contribute about 0.1 mEq./L. of plasma to the excess "R" value. Blood lactate levels in somewhat older infants were found by Brehme[35] to be 8 mg. per cent above adult levels, which would contribute only about 1.2 mEq./L. of plasma to the "R" value. Thus, the products of anaerobic glycolysis account for only one quarter of the excess "R" value. Leopold and Bernhard[36] found no relation between lactate level and CO_2 combining power in older children.

The data of Tables II-V indicate that buffer base rises steadily after birth, but that at 24 hours it is still below the normal adult level of 49 mEq./L. (though higher than the maternal level). Reduction of buffer base means, by definition, metabolic acidosis. However, it is not necessary to assume that this acidosis is a result of increased capacity of the fetus and newborn for anaerobic glycolysis. Holaday and associates[37] have demonstrated in anesthetized man and animals that CO$_2$ retention is capable of producing a prolonged fall in buffer base by a mechanism yet to be elucidated. The work of Singer and his colleagues, quoted by Dripps and Severinghaus,[38] indicates the possibility of migration of hydrogen ion from the cell to the extracellular fluid during CO$_2$ retention. It is possible that CO$_2$ retention during parturition induces a similar change in the human infant. Further investigation of the acid-base balance of the fetus in utero is necessary to answer this question.

SUMMARY AND CONCLUSIONS

In evaluating the significance of the low Pco$_2$ and CO$_2$ content in the blood and plasma of newborn infants, consideration should be given to the fact that this state also exists in the pregnant woman during the last trimester. Interpretations of the status of the newborn infant's respiratory drives and acid-base metabolism made with respect to normal adult values may be misleading.

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REACTION OF 150 INFANTS TO COLD FORMULAS

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THE young mother asked, "Will cold milk hurt my baby? I gave him an ice-cold formula the other night. I was so tired I didn't realize what I was doing, but he liked the milk cold and now prefers all his bottles straight out of the refrigerator. Will it hurt him?"

The baby, 6 weeks old, seemed perfectly healthy and happy, so what was the answer to her question? After this same inquiry came from several other mothers following similar incidents, I began to ask questions. I soon found that quite a few mothers had stumbled into this same practice of giving cold formulas, and that a surprising number of infants were being given ice cream, all with obvious enjoyment, and none with any apparent harmful results.

Questions presented themselves for further study:

1. Is the practice of warming formulas based upon necessity or tradition?
2. What is the acceptance rate on the part of young infants to cold formulas?
3. Do cold formulas have any harmful effect on the babies?

Information on these points would be important to mothers who prepare about 1,400 bottles of formula during the first 8 months of the baby's life. Do they need to warm all those bottles? This question becomes still more urgent in the middle of the night and on trips. It is of importance to us as physicians to know whether cold formulas are harmful to infants.

METHODS

Since no studies could be found in medical literature dealing with the problem of giving cold formulas to infants, I began with my own patients in private practice. As the mothers would bring their babies to the office for their regular monthly examinations I would ask, "Mother, wouldn't it be nice if you didn't have to warm all those bottles?" She would respond, "Oh, that would be wonderful! Tell me more." I would then suggest that if she would warm each bottle a little less each time, before long the baby might prefer his bottle either cool or straight out of the refrigerator. No time schedule was suggested and bottle temperatures were not taken. The enthusiasim with which the mothers acted on this suggestion was remarkable.

At the monthly visits, the infants were weighed, measured, and given a complete examination, and the mother reported on her experiences. The mothers described a cool formula as one that had been removed from the refrigerator and allowed to stand in the kitchen "until the chill was off" or "until it approached room temperature." A cold bottle was one taken directly from the refrigerator and given to the baby. Usual temperatures of formulas from refrigerators are about 40° F. or 5° C. All of the babies were changed gradually from warm to cool to cold bottles.

There are 150 infants in my private practice who have been offered cold formulas. Of these, 69 are males, 81 females. All are white except for 1 Negro and 1 Mexican. Their ages range from 15 hours to 7 months.

ACCEPTANCE RATE

TABLE I. ACCEPTANCE OF COOL AND COLD FORMULAS BY 150 INFANTS

AGE GROUP	NUMBER	REFUSED COOL OR COLD MILK	ACCEPTED COOL MILK	ACCEPTED COLD MILK	AVERAGE INTERVAL FOR CHANGE (DAYS)
1 day to 3 weeks	43	3	17	23	7
1 to 3 months	68	6	20	42	6
3½ to 7 months	39	7	4	28	7
Totals	150	16	41	93	average 6·7

TABLE II. SUMMARY OF WEIGHT CURVES OF 120 INFANTS CHANGED TO COOL OR COLD FORMULAS, AND FOLLOWED FOR AN AVERAGE OF 6.7 MONTHS AFTER THE CHANGE

AGE GROUP	NUMBER	CONSISTENT WEIGHT CURVES			WEIGHT CURVE DEVIATIONS	
		ABOVE AVERAGE	AVERAGE	BELOW AVERAGE	UPWARD	DOWNWARD
1 day to 3 weeks	38	18	15	1	4	0
1 to 3 months	56	34	16	3	3	0
3½ to 7 months	26	16	8	2	0	0
Totals	120	68	39	6	7	0

It was noted that the acceptance rate for cold formulas varied from about 50 per cent (23 of 43) for the very young infants to about 75 per cent (28 of 39) in the older group. For the whole group of 150, the acceptance rate for cool or cold formulas was 89 per cent, within an average period of one week.

EFFECT OF UNHEATED FORMULAS ON INFANTS

There were 11 infants in the group who could be classified as "gassy" or "colicky." Two of the mothers were convinced that the cold formulas had "cured the colic" for their babies. In the other 9 there was apparently no change. In 3 other babies, not in this group, the mothers felt that the cold formulas had caused the babies to have "gas pains," so no further effort was made to give them cold bottles. This group is too small to be of significance.

In assessing the developmental progress of the 134 infants who accepted cool and cold formulas, a complete examination was made each month. Weight records were plotted on a chart with the average curve starting at 7½ pounds, curving up to 14 pounds at 5 months, and 20 pounds at 12 months. More attention was given to a consistent weight curve parallel to the average than to actual poundage. Weight curves were classified as: (a) consistently above average, both before and after the change to unheated formulas; or (b) consistently average, before and after the change; or (c) consistently below average, before and after the change.

All of these curves were considered satisfactory, if consistent, and if the infant's general condition was good. Search was made for deviations in the weight curve either upward or downward that coincided with or followed a change to unheated formulas.

All of the weight curves were consistent before and after the change to unheated formulas, except for 7 infants who had a marked deviation upward in their weight curves coinciding with the change. No infant had a downward deviation.

EFFECT ON BODY TEMPERATURE

One mother who had just been delivered of her second baby requested, "Please train my baby to take his formula cold while he is in the nursery; my first child did so well on cold formulas." This presented an opportunity to record body temperatures after taking a cold formula. The infant (6 pounds, 11 ounces) had received one warm bottle when he was 12 hours old, taking it well. At the age of 15 hours, rectal temperature was taken and an ice-cold formula offered, which he also took well (about 2 ounces). Rectal temperatures were then taken immediately after feeding, and at intervals of 5, 10, and 30 minutes later. This was repeated for the next 8 cold formulas, average 1½ to 2 ounces each. In the 25 postformula temperatures there was no reduction of temperature in 12; a reduction of 0.2 degree in 6, a reduction of 0.4 degree in 1, and a reduction of 0.6 degree in 2, a reduction of 0.8 degree in 2, and an elevation of 0.2 degree in 1.

This infant started to gain weight on the second day. At the age of 13 days, the weight was 7 pounds, and at 1 month it was 8 pounds, 10 ounces, with general condition excellent.

CONCLUSIONS

1. In a group of 150 infants, cool or cold formulas were accepted by 89 per cent.

2. In 120 of the infants accepting cool or cold formulas and followed for an average of 6.7 months, development proceeded normally.

3. No harmful effects could be found in the infants accepting the cool and cold formulas.

THE MYELOPROLIFERATIVE SYNDROME IN CHILDREN

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FIBROSIS of the bone marrow with extramedullary hematopoiesis is occasionally associated with certain hematologic disorders including polycythemia vera, agnogenic myeloid metaplasia, and erythroleukemia. It has been proposed that these anatomic changes represent a syndrome of chronic demand upon hematopoiesis resulting in "en masse" proliferation of bone marrow.[1]

The following synonyms emphasize the striking number of pathologic interpretations applied to this syndrome: (1) subacute myelosclerosis, (2) leukoerythroblastic anemia, (3) osteosclerosis, (4) chronic nonleukemic myelosis, (5) osteosclerotic myelopathy, (6) aleukemic myelosis, (7) agnogenic myeloid metaplasia, and (8) erythroleukemia.

There is no relationship with the osteosclerotic process of Albers-Schonberg, in which there is excess calcification of bony cortex, absence of bone lamellae, defective ossification, and absence of osteoblastic activity. This contrasts with primary myelofibrosis where the marrow is obliterated by fibrous or bony tissue and the cortex is spared with little or no effect.[2]

Disorders in myeloproliferation are usually described in older age groups. Less than a dozen instances of this disease have been identified and reported in pediatric subjects. The purpose of this paper is to report the finding of myelofibrosis in 2 children, and to review and discuss the literature concerning this disorder.

CASE REPORTS

Case 1.—A 23-month-old white female infant with mongolism was hospitalized in Texas Children's Hospital because of anemia for three months and a respiratory infection for one month which had not responded to treatment with iron-cobalt mixture, penicillin, and streptomycin.

The mother was 26 years of age. Pregnancy, labor, and delivery had not been complicated. Mongolism was recognized shortly after birth. Subsequent motor and mental development was slow. The diet was limited principally to milk and cereal. There were no previous illnesses and no previous medications. Immunization included a single inoculation of diphtheria-pertussis-tetanus.

By physical examination, pallor was conspicuous. The liver extended 2.0 cm. and the spleen 3.0 cm. below the respective costal margins. Hemoglobin was 4.4 Gm./100 c.c. The red blood cell count was 1,270,000, and the white blood cell count 5,400. The differential count contained 1 blast cell, 5 promyelocytes, 12 myelocytes, 24 metamyelocytes, 12 polymorphonuclear cells, 3 monocytes, and 43 lymphocytes. The reticulocyte count was 0.5 per cent. After a whole blood transfusion, the hemoglobin rose to 8.0 Gm./100 c.c., and she was discharged.

She was readmitted three weeks later because of episodes of fever lasting 12 to 24 hours. Fever was refractory to therapy during the week before rehospitalization.

The physical examination was unchanged. Hemoglobin was 6.7 Gm./100 c.c. The red blood cell count was 2,400,000 and white blood cell count 23,450. About 60 per cent of the white

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blood cells were identified as blast cells. Red cells were hypochromic. Capillary bleeding time was 2 minutes, 20 seconds and the capillary clotting time was 4 minutes, 45 seconds. The platelet count was 117,000 and the clot retraction was normal. The serum bilirubin was 0.3 mg./100 ml. Febrile agglutinations were negative. The heterophile antibody was positive 1:7. Urinalysis was normal. The serum VDRL was negative. Two bone marrow aspirations were so completely made up of peripheral blood that they were unsatisfactory for diagnosis. A diagnosis of acute leukemia was made on the basis of the findings in the peripheral blood film.

She was given a blood transfusion and cortisone, 200 mg. daily. Cortisone was decreased to 75 mg. daily after four days. Irritability and somnolence increased. Hemoglobin dropped to 4.8 Gm./100 ml. but rose to 10.3 Gm./100 ml. after blood transfusion. The white blood cell count was now 200,000.

The final hospitalization was two weeks later, because of persistent fever, paroxysmal coughing, and small ulcers in the mouth. Hemoglobin was 12.6 Gm./100 ml. The white blood cell count was 9,600 and all cells were described as blasts. *Pseudomonas aeruginosa* was cultured from the blood and pharynx. She died two days after admission.

Autopsy Report.—The physical features of mongolism were present.

The right and left lungs weighed 160 and 100 Gm., respectively. An area of firm consolidation containing multiple firm, red-gray nodules was found in the dependent portions of each lung. Each pleural space contained about 75 ml. of cloudy yellow fluid and a few thin, friable adhesions.

The spleen weighed 310 Gm. in contrast to an average of 33 Gm. for this age. The capsule was purple-gray and intact. The cut surface was fleshy and fibrotic with a semitranslucence of the trabecular structure. Lymphoid follicles were not apparent grossly. The marrow space of a rib was homogeneously pale yellow and contained no visible normal marrow. The lymph nodes were enlarged but discrete, and their cut surfaces were homogeneous without obvious change from normal. The liver weighed 570 Gm. in contrast to an average of 394 Gm. The lobular architecture was prominent.

There was a chronic gingivostomatitis. Multiple petechiae were present in the mucosa of the stomach, small intestine, and colon.

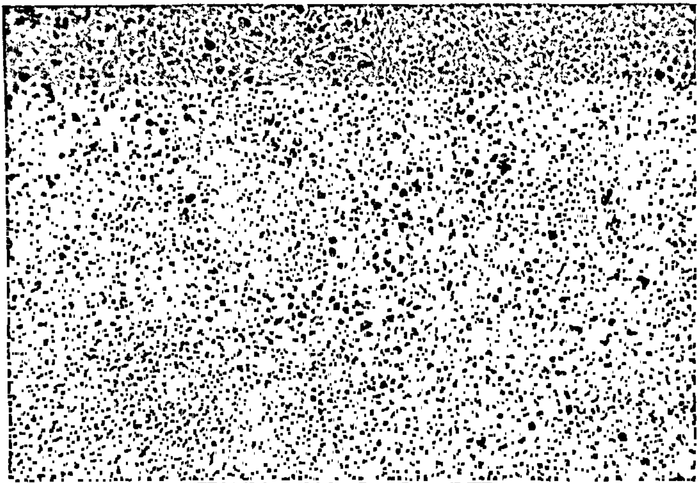
A Pseudomonas of unidentified species was cultured from the lung and the heart's blood.

Microscopically, there was extensive pulmonary edema with numerous deposits of fibrin in which clumps of bacteria were present. Focal areas of complete necrosis of the lung were associated with a striking paucity of acute inflammatory cells. Many large mononuclear cells and a few large bizarre multinucleated forms were present.

The red pulp of the spleen was filled with a remarkably pleomorphic cell population (Fig. 1). The most conspicuous cell was large and irregular with both multinucleated and multilobed nucleus forms. In both types, the nuclei were deeply basophilic and rarely contained nucleoli, and the cytoplasm was deeply eosinophilic and finely granular. Many immature granulocytes were present. A few small foci of erythropoiesis were present. Several small lymphoid follicles were present and, in some areas, remnants of a follicle which had been replaced by myeloid elements could be identified. Deposits of collagen in a loose fibrillar pattern about the lymphoid follicles were identified in the Mallory's aniline blue stain. In addition, the reticulum structure was accentuated throughout the spleen. Nests of large, bizarre cells in groups of three or four were surrounded by a prominent reticulum band. A moderate quantity of iron was identified by the Gömöri's iron stain.

A few of the large cell types were seen within the sinusoids of the liver. The architecture of the liver was well preserved, however, and there was no cellular infiltration.

Fig. 1.



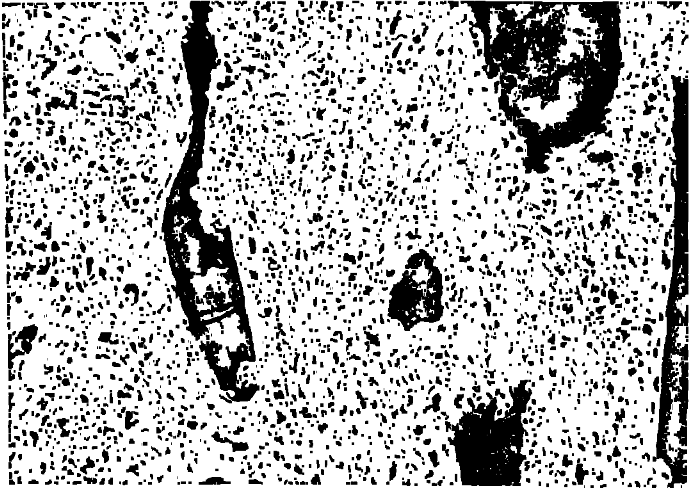


Fig. 2.

Fig. 1.—In the spleen of Case 1 there is a prominent myeloid metaplasia with many megakaryocytes. A depleted lymphoid follicle is present.

Fig. 2.—In the marrow of the rib of Case 1 there is a paucity of cells associated with a thickening of reticulum and many megakaryocytes.

The supraclavicular lymph nodes were distorted by extensive hemorrhage and, in addition, contained large colonies of bacteria. A few large multinucleated cells were also present within the substance of the node. Reticulum cells were prominent in the mediastinal and mesenteric nodes. Lymphatic vessels were dilated and filled with mononuclear and a few multinucleated cells, although the stroma showed marked lymphoid depletion. A mediastinal node contained an area of necrosis associated with bacterial colonies.

There was a general replacement of bone marrow substance by a marked degree of fibrosis (Fig. 2). Trabeculae were diminished considerably in number and size. There was little change in the cortical bone. Proliferation of reticulum and increase of collagen content were identified in this area. No free iron was found. A few islands of cellularity consisted solely of clumps of poorly differentiated mononuclear and large multinucleated cells.

A single, small, subcortical hemorrhage was present in the cerebral cortex with no associated cellular response.

Case 2.—A 13-month-old white female infant was hospitalized because of anemia. She had had repeated episodes of otitis media requiring several myringotomies. The mother had had a splenectomy at 12 years of age because of ''Banti's disease,'' and had since received iron medication.

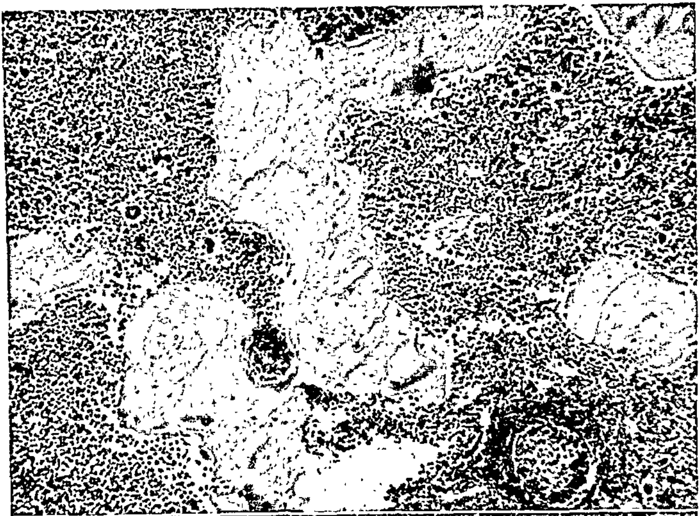
The patient was pale but otherwise vigorous. The spleen was palpable 5.0 cm. below the left and the liver 3.0 cm. below the right costal margin.

Hemoglobin was 5.9 Gm./100 ml. and the red blood cell count was 3,240,000. Urinalysis was negative. The VDRL was negative. The capillary bleeding time was 3 minutes, 45 seconds. Clotting time (capillary) was 4 minutes, 20 seconds. Osmotic fragility of the red cells was the same as the control. A bone marrow aspiration was diluted with peripheral blood and was not diagnostic. She was discharged from the hospital and readmitted three weeks later. Physical examination disclosed no change.

Hemoglobin was 11.3 Gm./100 ml. Prothrombin concentration was 100 per cent of normal. Serum bilirubin was 0.5 mg./100 ml. Total serum protein was 7.4 Gm./100 ml. with 5.0 Gm. of albumin and 2.4 Gm. of globulin. Thymol turbidity was 5.8 units. The fasting blood sugar was 80.0 mg. and blood urea nitrogen 12.0 mg./100 ml. Roentgenograms showed normal esophagus, skull, knees, and pelvis. A bone marrow biopsy showed moderate, generalized hyperplasia with a few small lymphoid follicles (Fig. 3). She was discharged 4 days later.

During the following seven months she was hospitalized twice because of steady fall in the hemoglobin level. She was treated with whole blood transfusions each time. At the end of this time, she was hospitalized for splenectomy. Hemoglobin was 14.5 Gm./100 ml. White blood cell count was 13,750. Splenectomy and liver biopsy were performed under general anesthesia. The surgical specimen included congestive splenomegaly (Fig. 4), a single accessory spleen, and a hyperplastic lymph node. No abnormality was found in the liver. Four days after operation, she had fever of 104° F. and erythema and edema of the mucous membranes of the mouth and gums. White blood count was 7,200 with 31 per cent segmented neutrophils, 12 per cent band forms, 51 per cent lymphocytes, 2 per cent monocytes, and 4 per cent eosinophils. The following day a confluent rash was present on the entire body. Suboccipital lymphadenopathy was noted also, and a diagnosis of rubella was made. By the seventh hospital day, however, fever was still present and generalized lymphadenopathy was present. The skin rash disappeared the following day, lymphadenopathy

Fig. 3.



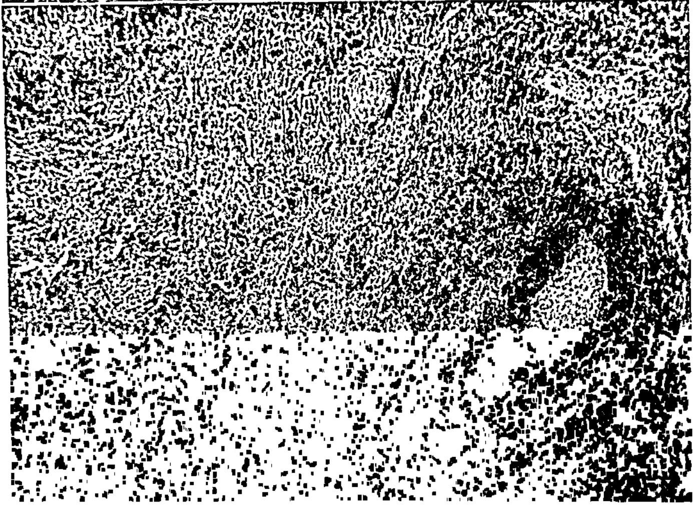


Fig. 4.

Fig. 3.—The surgical bone biopsy of Case 2 contains a cellular marrow whose structure is marred only by the presence of a single lymphoid follicle.

Fig. 4.—In the surgically excised spleen of Case 2 there is a moderate fibrosis of the red pulp associated with a normal pattern of lymphoid follicles.

was the same, but her general condition was such that she was discharged for home care.

During the next three days new skin lesions appeared, and these suggested varicella. Her course was not otherwise remarkable until the end of the third day when she began to vomit and became cyanotic. Vascular collapse developed rapidly and she died en route to the hospital.

Autopsy Report.—Several well-circumscribed ecchymoses were present on the thigh, back, and neck. The lungs were diffusely edematous and firm with decreased crepitation. Small, firm, gray-brown, granular areas were scattered irregularly throughout the lung parenchyma. The splenic and portal veins showed no gross abnormality. The marrow space of a rib was red-brown and moist. Lymph nodes in the retroperitoneal, mesenteric, and mediastinal regions were enlarged to 3.0 cm. Their cut-surface was gray-brown and homogeneous. The liver was enlarged to almost twice the average weight for this age. The surface of the liver contained many small, white, granular areas scattered irregularly at intervals through the parenchyma. These had a maximum dimension of 0.2 cm.

Microscopic examination of the lung showed large, poorly circumscribed areas of edema and necrosis with a striking paucity of inflammatory reaction. Large masses of rod-shaped bacteria were present within the alveoli. Only a few mononuclear cells were found.

Within the liver, isolated foci of complete necrosis without inflammatory reaction were identified. Rod-shaped bacteria, similar to those found in the lung, were also present in these areas of the liver.

The marrow space of the rib was markedly depleted of all marrow elements (Fig. 5). There were clusters of mature lymphocytes with focal aggregation into germinal centers. There were many large cells with multilobed nuclei identified as megakaryocytes, and other large cells identified as young fibroblasts.

DISCUSSION

The diseases in these infants were manifest by two different hematologic responses. They terminated with a common anatomic lesion consisting of decreased cellularity, megakaryocytic hyperplasia, and fibrosis of the bone marrow. The stimulating factor is unknown but is considered a myelo-stimulatory factor which may be activated by a wide variety of agents.

The illness of the first patient resembles most closely that of leukemia, particularly with respect to the presence of circulating immature cells. The second appears to have had a hypersplenic syndrome associated with a congestive splenomegaly of undetermined etiology.

It is thus suggested that myelofibrosis can be the evolutionary end product of a disease state, the nature of which creates a chronic demand on the bone marrow which then becomes functionally incapable of meeting these demands. This results in functional failure of the bone marrow and this is expressed anatomically by myelofibrosis and myeloid metaplasia.

Death due to the underlying disease process may occur in any phase of the syndrome. Therefore, tissue examination, depending upon the stage of the disease, reveals diffuse hyperplasia, hypoplasia, myeloid metaplasia or fibrosis.

Eight cases of myelofibrosis in childhood were discovered in the medical literature. The clinical data of these children have been summarized in Table I. Six of the 8 patients were female, and all were under 3 years of age. Splenomegaly and hepatomegaly were prominent. Anemia was moderate to severe. The white blood cell count varied from leukopenia to leukocytosis. Immature white cells in the peripheral blood were as frequent as immature red cells. Careful scrutiny of peripheral blood films occasionally revealed a few megakaryocytes. Bone marrow fibrosis was recognized by biopsy in some instances and determined at autopsy in others.

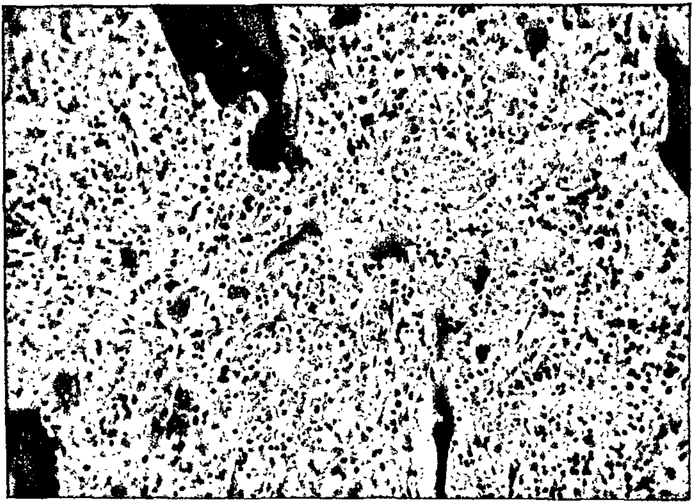


Fig. 5.—On the post-mortem bone marrow of Case 2 there is a striking paucity of cells with retention of the reticulum structure and a prominence of megakaryocytes.

The process of fibrosis of the marrow has been described following x-radiation, tuberculosis infection, Paget's disease, metastatic neoplasm, multiple myeloma, septicemia, and benzene.[3] It has been proposed that focal necrosis of the marrow is initiated which is followed by reactive hyperplasia of the stroma resulting in the sclerosis.[4, 5]

Dameshek[1] made the interesting editorial comment that the bone marrow can proliferate "en masse" as well as along individual cell lines. Thus, fibrosis may be a type of proliferation such as seen in leukemia or polycythemia.

The relationship between myelofibrosis and the myeloid metaplasia may be one of several possibilities: (1) purely fortuitous; (2) myelofibrosis is the result of a primary blood disease, (3) blood diseases are the result of myelofibrosis, (4) the two features are actually similar results of the same noxious agent functioning at two discrete sites,[6] and (5) extramedullary hematopoiesis is a compensatory response.[7, 8] The unusually large number of megakaryocytes has been attributed to an exaggerated physiologic response to a marked decrease in efficiency of platelet formation.[9]

It is only with acceptance of the fourth possibility that this disease can

TABLE I. A SUMMARY OF THE FINDINGS FROM THE

NO.	AUTHOR	AGE (MONTHS)	SEX	SPLEEN	LIVER
1	Rosenthal and Erf[3]	$\frac{4}{12}$	Female	Enlarged	Enlarged
2	Rosenthal and Erf[3]	$\frac{4}{12}$	Female		
3	Rosenthal and Erf[3]	10	Female	Enlarged	Enlarged
4	Rosenthal and Erf[3]	$1\frac{4}{12}$	Female	Enlarged	Enlarged
5	Erf and Herbut[19]	2	Female	Enlarged	Enlarged
6	Churg and Wachstein[17]	$2\frac{8}{12}$	Female		
7	Block and Jacobson[7]	$2\frac{6}{12}$	Male	Enlarged	Enlarged
8	Wood and Andrews[2]	$2\frac{6}{12}$	Male	Enlarged	Enlarged

be considered a part of the myeloproliferative group.

It has been suggested that splenectomy, while causing no demonstrable hematologic improvement, does not necessarily prove deleterious to the course of the disease.[10] The implication is that metaplasia is not a compensatory mechanism, but a basic feature of the process.

The resemblance of the disease to leukemia may be striking. Suggestions have been made concerning a possible relationship which parallels the "en masse" proliferation of Dameshek. These include the idea that the fibrosis is due to neoplasia of the immature multipotential mesenchymal cell.[11-15]

The histology of the spleen resembles that of granulocytic leukemia although there are differences.[16] The lymphoid follicles in leukemia are obliterated. The lymphoid follicles in myeloid metaplasia are preserved, but occasionally contain a fibrotic process similar to that in the marrow. Many megakaryocytes are present in myeloid metaplasia. There is no invasion by sheets of uniform cells which is unlike leukemia.

Churg and Wachstein described 97 cases of leukemia including 6 in which there was myelosclerosis.[17] In striking contrast to this, a much higher incidence of sclerosis was found in what they described as "non-leukemic myelosis." Furth's[18] definition of leukemia states that "the essential change in leukemia resides in the cell and consists of an acquired inability of immature leukocytes to respond to forces normally regulating their proliferation and maturation."

There is no apparent escape from normal regulation, as defined by Furth, when marrow tissue responds by necrosis to a noxious agent followed by fibrosis. Proliferation of the remaining marrow may or may not be along normal lines of evolution, and this depends upon whether or not the stimulus to necrosis was leukemia. It is suggested that leukemia can terminate with myelofibrosis but so can any disease in which bone marrow failure is a component.

SUMMARY

The clinical history and autopsy findings are presented in 2 children with disease of bone marrow and spleen. In one, there was myelofibrosis of the bone marrow with myeloid

MEDICAL LITERATURE OF EIGHT CHILDREN WITH MYELOFIBROSIS

HEMOGLOBIN	RBC (AS 10^6)	WBC (AS 10^3)	IMMATURE FORMS IN THE PERIPHERAL BLOOD	BONE MARROW	
				BIOPSY	AT AUTOPSY
20%	1.12	10.0	Granulocytic and erythrocytic	Fibrosis	
16%	1.05	7.1	Granulocytic	Fibrosis	
12%	1.09	1.9		Fibrosis	
22%	1.5	1.7	Granulocytic and erythrocytic	Fibrosis	Fibrosis
21%	1.6	6.0 7.2	Erythrocytic	Fibrosis Fibrosis	Fibrosis
9.0 Gm./100 ml.	3.9	17.0	Granulocytic and erythrocytic	Fibrosis	Fibrosis
55%	1.1	15.0	Granulocytic and erythrocytic		Fibrosis

metaplasia of the spleen. The second patient had a change from hyperplasia of the bone marrow to hypoplasia. In each instance there was a prominence of megakaryocytes. Death was associated with disseminated agranulocytic abscesses.

It is proposed that these individuals represent phases in the development of myelofibrosis in which bone marrow progresses from hyperplasia to fibrosis and myeloid metaplasia occurs in the spleen under the influence of unknown forces.

Eight other instances of this syndrome in infants and children are tabulated.

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VARIATION IN THE ROENTGENOGRAPHIC DENSITY OF THE OS CALCIS AND PHALANX WITH SEX AND AGE

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INTRODUCTION

ALTHOUGH the marked changes that occur in the size and shape of the skeleton during growth can be observed by the use of roentgenograms,[1] the concomitant changes in the bone mineral concentration, which may also occur during growth, have not been extensively studied due chiefly to the lack of quantitative roentgenographic techniques. With the development of photodensitometric techniques, quantitative measurements of the bone mineral concentration have become possible.[2, 3, 4] The application of this technique for the study of osseous disorders and the normal variation in bone density found in man is relatively unexplored. McFarland[5] published bone density values for the os calcis of 1,200 normal persons of all ages and both sexes. A study with aged subjects (60-98 years) showed that no significant photodensitometric differences occurred in the os calcis and phalanx 5-2.[6] In the latter two studies, the apparatus used was the same as that employed in the present report. Using a different technique and apparatus, Mainland reported that no significant difference in the roentgenographic density occurred in the os calcis,[7] the radius, the lunate, the capitate and the metacarpal bones due to age or sex. Phalanx density, however, showed a decrease with increasing age.[8]

The investigation of photodensitometric bone values in normal subjects according to age and sex would provide a basis for determining the influence of these factors on bone density. As the initial phase in such a study, the results of bone density evaluations made from roentgenograms of the os calcis and phalanx 5-2 in several hundred boys and girls are presented.

METHODS

Roentgenograms of the left os calcis and phalanx 5-2 were taken of subjects in various geographical locations. The number of subjects from each location is shown in Table I.

TABLE I. THE GEOGRAPHIC DISTRIBUTION OF THE SUBJECTS

LOCATION	OS CALCIS FILMS		PHALANX FILMS	
	MALE	FEMALE	MALE	FEMALE
Washington	177	164	173	156
Montana	38	46	41	53
New Mexico	20	26	19	25
Pennsylvania	482	506	304	74
Miscellaneous (U.S.)	21	4	87	87
Totals	738	746	624	395

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Film Exposure Technique.—The bone density computing apparatus, the x-ray technique, and the film developing procedure are standardized and have been described in previous publications.[2, 9] In brief, 8 × 10 no-screen film in cardboard holders are exposed at 55 KVP. The MAS is varied with focal film distance and size of object. The computing machine is used to evaluate the mass of bone in a cross-sectional slice of bone and surrounding flesh from the roentgenographic image. The anatomic section evaluated is referred to as a trace path. The films require that a standardized wedge be exposed on the film adjacent to the anatomic part of interest.

The Standard Wedge.—The standard wedge is precision tooled from an alloy consisting of 92.8 per cent of aluminum and 7.2 per cent of zinc. It is 14 cm. long, and 1.4 cm. wide at the widest part with a slope of 0.1. A frame of the same material holds the wedge. Several of these wedges have been made from a single mass of homogenous material to ensure uniformity between wedges and to permit direct comparison to be made by different investigators who use this technique. The x-ray absorption properties of the wedge material approximates that of bone ash, has good mechanical and chemical stability, and is not difficult to machine.[10]

Bone Sites Evaluated.—The value for the os calcis is obtained from measurements made along a trace path extending from the posterior-superior angle to the anterior-inferior angle of the bone image. Three cross-sectional slices of the phalanx are evaluated, one at the distal and proximal ends and one at the center. The values of the distal and proximal ends are usually averaged and the result is termed the bone density coefficient for the phalanx end trace paths. The values for each end could be presented separately. The center cross-sectional slice is termed the phalanx center trace path.[9]

Soft Tissue Correction.—To evaluate the density coefficient or mass coefficient of bone sections in living subjects, the absorption of x-radiation by under- and overlying soft tissue must be taken into account. The method which has been developed will be explained by reference to Fig. 1. In this case the roentgenogram has been made at right angles to the face of the diagrammatic object. The flesh alone is responsible for the roentgen ray absorption in Areas 1 and 4, whereas bone plus under- and overlying soft tissue are responsible for the absorption in Areas 2, 3, and 5. Therefore, the portions of the trace shown in the lower part of the diagram can be assigned, respectively, to soft tissue and to bone and soft tissue. Then, on the assumption that the soft tissue areas in the regions 2 and 3 underlying and overlying the bone have the same absorbing properties, a soft tissue correction term is subtracted from the area of the central trace, designated as 2, 3, 5, to determine that portion of the trace area which is due to the x-ray absorption by bone alone. The mass coefficient or density coefficient of the bone is then calculated. The term density coefficient is used rather than density, as the value obtained with the machine has to be multiplied by a constant to give the density.

The density coefficient of an object (bone section or soft tissue section) is defined as the number of grams of the aluminum-zinc alloy, which in a similar geometric shape would absorb the same amount of x-radiation as the object, divided by the volume of the object in cubic centimeters. When the volume of the object is not considered, the mass coefficient is obtained.

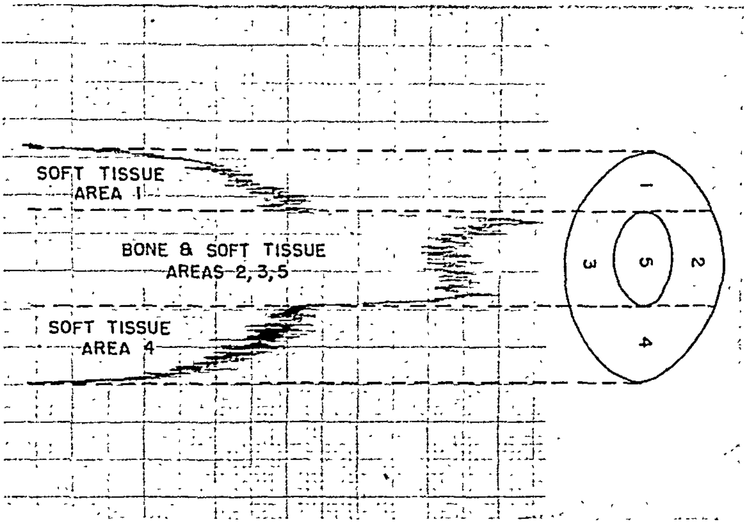

Fig. 1.—Diagrammatic representation of a bone and surrounding flesh with a photodensitometer trace (see text for explanation).

Referring again to Fig. 1, the following gives the computation procedure:

1. The total volume of soft tissue in portions 1 and 4 of the cross-sectional slice is estimated; the shape and dimensions of the soft tissue are estimated from the image on the film.
2. The volume of bone in portion 5 of the cross-sectional slice is estimated also from measurements on the film.
3. The total volume of soft tissue in portions 2 and 3 of the cross-sectional slice is estimated similarly.
4. The average density coefficient of portions 1 and 4 is found by dividing the mass coefficient (determined from the counter reading of the computing machine) of these portions by their volume as estimated in step 1. The result is termed the x-ray density coefficient of soft tissue.
5. The x-ray mass of portion 5 (bone) is found by subtracting from the total mass of portions 2, 3, and 5 (as determined by the computing machine from the central portion of the trace) the x-ray mass of overlying and underlying soft tissue, portions 2 and 3 of the cross-sectional slice. The mass of sections 2 and 3 is determined by multiplying the soft tissue x-ray density from step 4 by the estimated volume of soft tissue in portions 2 and 3 (from step 3).

The foregoing procedure has been in use for several years. Each bone site requires a different calculation for estimating the volume. The methods presently available for estimating the volumes of the various portions of the cross-sectional slice are more time consuming and considerably less precise than the mass determinations made from the film by the computing machine. Methods of estimating bone and soft tissue volumes, however, are being improved constantly.

The data resulting from the film evaluations were subdivided on the basis of the bone site evaluated, the age and the sex of the subjects. Only films of normal, white subjects which were satisfactory from the standpoint of technique were included. The ages of the subjects used in this study ranged from 7-20 years (Table II).

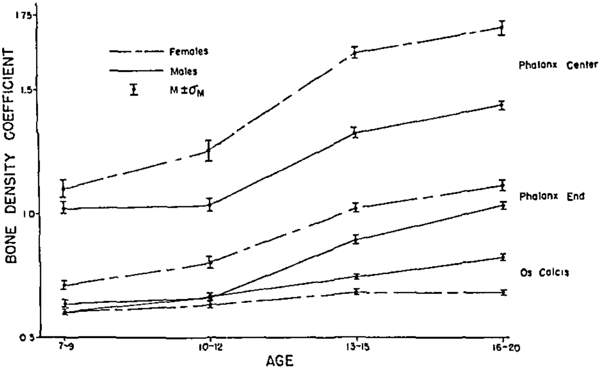

Fig. 2—The variation in bone density coefficients of the os calcis and phalanx trace paths with sex and age.

RESULTS

The results were grouped by sex and trace path corresponding to the following age ranges of the subjects; 7-9 years, 10-12 years, 13-15 years, and 16-20 years. The mean bone density coefficient and the standard deviation for each group was then calculated and tabulated as shown in Table II. The interrelationships of the group values are graphically shown in Fig. 2 which presents the mean values and the standard error for each group.

Analysis of the data revealed that (1), with the exceptions noted below, the mean bone density coefficient for each trace path increases significantly with age ($P > .001$). The exceptions were, that there was no significant difference in the phalanx center trace path for males between the 7-9 year group and the 10-12 year group, nor for the os calcis trace path of the females between the 13-15 year group and the 16-20 year groups; (2) the values for the female phalanx are significantly greater ($P > .001$) than for the males of the same age; (3) the values for the male os calcis in the 13-15 and 16-20 year groups are significantly greater at the 0.001 level than for the females of the same age, while the male os calcis values are significantly greater at the 0.01 level in

TABLE II. MEAN DENSITY COEFFICIENTS OF THE OS CALCIS AND PHALANX OF SUBJECTS AGED 7 TO 20 YEARS

AGE GROUP	OS CALCIS						PHALANX END						PHALANX CENTER					
	MALES			FEMALES			MALES			FEMALES			MALES			FEMALES		
	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.	MEAN	SD	NO.
7-9	0.60	0.09	138	0.60	0.09	139	0.64	0.11	77	0.71	0.16	97	1.02	0.23	77	1.10	0.21	97
10-12	0.67	0.10	183	0.63	0.08	138	0.66	0.16	101	0.80	0.18	56	1.03	0.28	101	1.25	0.30	56
13-15	0.74	0.10	254	0.68	0.10	296	0.89	0.21	225	1.02	0.18	135	1.32	0.30	225	1.64	0.22	135
16-20	0.82	0.05	163	0.68	0.09	173	1.03	0.19	221	1.11	0.18	107	1.43	0.24	221	1.74	0.31	107

the 10-12 year group. However, there is no noticeable sex difference for this trace path in the 7-9 year groups; (4) the phalanx center trace path, which contains mainly compact bone, shows the highest values with the phalanx end trace paths and os calcis giving lower values, respectively; and (5) the range of values is much greater for each phalanx trace path than for the os calcis trace path.

DISCUSSION

The results of the present study indicate that sexual dimorphism exists in young adults with respect to bone density coefficients obtained from roentgenograms of the os calcis and phalanx 5-2; females have denser phalanges than males in the age groups studied, while males have a denser os calcis. The concept of sex and age differences in bone density has been demonstrated in rats by others using water displacement techniques; females had denser femurs than males and young animals had denser bones than old animals.[11]

Some of these observations may be explained by the earlier maturation of the female skeleton. The earlier closure of the epiphyses in the female and the consequent curtailment of growth appears to accompany an increase in bone mineral concentration as indicated by the higher bone density coefficients observed for the female phalanx. However, this does not account for the higher values found for the male os calcis. It seems unlikely that greater activity on the part of the males could account for this difference. It is conceivable that a different rate of mineral accretion occurs in different bones influenced by hormonal and genetic factors. In mice, for example, it has been shown that estrogen administration induces a hypercalcification of the skeleton in general, while the pubic bones undergo resorption.[12]

The gradual increase in bone density coefficients in both sexes with age appears to reflect classical growth patterns. Prepuberal "density" spurts apparently occur in the phalanx, as can be seen in Fig. 1, between the 10-12 and 13-15 year age groups. An increasing divergence of the mean os calcis values between the males and females is also clearly indicated in the same figure. It should be pointed out that while, in general, the mean bone density coefficients for each trace path increase significantly with age and differ significantly by sex, the magnitude of the standard deviations is such that an individual set of values cannot serve to designate the sex and age of the subject except in extreme cases.

The relationship of the values in the 16-20 year groups, shown in Fig. 2, suggest that the density coefficients of the phalanx center and the os calcis will continue in a like manner for at least part of the third decade. This, of course, can only be shown by further study which is contemplated. It is interesting to note that Mainland[7] found no significant difference in the mean roentgenographic density of the os calcis of 42 men aged 20-54 years and 10 women aged 19-30 years, nor did his data for the men demonstrate a relationship for bone density and age. In a later study, the same author did observe a significant negative correlation with age in phalanx density for 41 men, but did not find a sex difference when compared with 10 women. Other hand bone values (radius, lunate, capitate, and metacarpal) were significantly lower for the women.[8]

Since the age ranges of the subjects, the soft tissue correction, the exposure standard and the densitometric apparatus are different, no direct comparison with Mainland's results can be made.

Williams and associates[13] who used an os calcis technique similar to that developed in this laboratory reported that, although in young normal adults the bone density values reflected the over-all past nutritional history of a subject, marked temporary changes in calcium intake did not alter the bone values.

The apparatus and technique employed in making these measurements are probably an important factor in considering the results. Indicative of the sound chemical and biological basis of the present technique is the correlation coefficient of 0.99 obtained when the mineral content of rat bone samples was compared with the x-ray mass coefficient of the same sample.[14] In addition, when values from x-ray films of intact rat femurs were compared with film values of the same femurs excised, a correlation coefficient of 0.95 was obtained.[15] While no well-controlled studies with human beings have been undertaken to establish the minimal detectable bone density changes which can be observed with this technique, studies with young rats have demonstrated that a severe change in the dietary calcium level can be detected in 7 days or less.[14]

An extension of these studies to cover the span of life is planned. The compilation of adequate bone density coefficient values based on age and sex may serve as standards in studying normal biologic variations. It may also be possible to detect pathologic conditions involving bone, and recovery from osseous disorders which are reflected in the measurable bone sites.

SUMMARY

Using standardized roentgenograms, the x-ray density coefficients of the left os calcis of 738 boys and 746 girls, and the middle and end sections of the second phalanx of the left fifth finger in 395 girls and 624 boys, all between the ages of 7 and 20 years, were measured. Significant differences in the mean values were noted which were associated with the age and sex of the subjects.

Analysis of the data revealed that:

1. The mean density coefficient of both bones increases significantly with age in both sexes except for the os calcis trace path of the females between age groups 13-15 and 16-20 and the phalanx center trace path of the males between age groups 7-9 and 10-12.

2. The phalanx shows higher density coefficients than the os calcis in both sexes.

3. The phalanx density coefficients of the females are significantly greater than those of the males of the same age and, except for the 7-9 year age group, the os calcis values of the males are significantly greater than those of the females.

The author wishes to acknowledge the labors of the late Dr. Walter N. Brown, Jr., formerly of this laboratory, who collected much of the present material.

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MUMPS MENINGOENCEPHALITIS IN CHILDREN

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MENINGOENCEPHALITIS, occurring in association with infection by the mumps virus, is an acute inflammatory disease of the central nervous system due in most instances to direct invasion of the brain and meninges by the specific virus.[1, 2] In some cases, however, the demyelinating or leukoclastic encephalitis found with mumps infection can be due to an allergic reaction by the brain occurring in the course of the disease.[2, 4-7] The central nervous system manifestations of mumps may precede, occur simultaneously with, or follow salivary gland involvement, or the central nervous system manifestations may occur without any other clinical evidence of mumps infection.[3, 8-16] This intriguing variability in the relationship between meningoencephalitis and other clinical forms of mumps led us to review our cases of mumps meningoencephalitis.

The purpose of this paper is to summarize our experience with 30 cases of mumps meningoencephalitis occurring in children under 14 years of age. Special emphasis will be placed upon the epidemiological, clinical, and serologic features of the disease.

METHODS AND MATERIALS

The records of all cases of mumps meningoencephalitis admitted to the Pediatric Service of the George F. Geisinger Memorial Hospital and Foss Clinic from January, 1951, to January, 1956, were reviewed. The Pediatric Service at this institution cares for children from birth to 14 years of age.

Lumbar punctures were done on admission on all of the patients. The cerebrospinal fluids were examined for cell, protein, and sugar content. Routine cultures for bacteria were done on all spinal fluids within 30 minutes of obtaining the specimens by inoculating the centrifuged sediment into brain-heart infusion broth with 2 per cent rabbit's blood and by streaking the sediment on blood agar plates made from blood agar base plus 5 per cent rabbit's blood. These cultures were all negative for bacterial growth after 48 hours' incubation at 37° C. under reduced oxygen tension. Ten of the 30 cases had acid-fast cultures made by streaking Petragnani medium with sediment of the cerebrospinal fluids. All of these cultures were negative for growth of acid-fast bacilli after 6 weeks' incubation at 37° C.

Intracutaneous tuberculin tests in concentrations of 0.0002 mg. and 0.005 mg. of purified protein derivative were done on all patients. The tuberculin tests were negative in every case except for one child who had a reaction at 48 hours greater than 6 mm. of edema to 0.005 mg. of PPD. This

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child was considered to be a positive tuberculin reactor. The patient's chest x-ray showed a pulmonary calcific density thought to represent a healed primary tuberculous complex. Cultures of the cerebrospinal fluid and gastric washings of this patient were negative for the tubercle bacillus and the clinical course of the illness was characteristic of mumps meningoencephalitis.

Paired sera were obtained from 24 patients for complement fixation tests against mumps antigens. All mumps serologic tests were performed by the Virus Diagnostic Laboratory of the Children's Hospital of Philadelphia.* The methods of preparing the mumps antigens and of performing the complement fixation tests which were used by this laboratory have been described.[13, 17]

A meningoencephalitis was considered to be present if the cerebrospinal fluid showed a pleocytosis of 10 or more leukocytes per cubic millimeter. The cases were diagnosed as mumps meningoencephalitis by the occurrence of clinical parotitis prior to, concomitant with, or shortly following the onset of the central nervous system manifestations or, in the absence of parotitis, by the presence of significantly rising complement fixing antibodies against the mumps virus in paired sera. Patients suspected clinically of having mumps meningoencephalitis but in whom pleocytosis of the cerebrospinal fluid did not occur were not included in this study.

The severity of illness was judged by the clinical findings on initial admission examination and by the subsequent hospital course. The children were described as not sick at all when they had no temperature elevations, were alert, and well oriented; as mildly ill when they had moderate temperature elevations, were only mildly lethargic, and well oriented; as moderately ill when they had higher fevers, were moderately lethargic and well oriented; as severely ill when they had high temperatures, marked lethargy or stupor, and disorientation or convulsions.

RESULTS

During this study, 30 cases of mumps meningoencephalitis were diagnosed. The age range of the children was from 2 to 14 years. The average age of the sick children was 7.4 years which approximates the reported age peak of 6 years for mumps parotitis.[11, 18] There was no difference in the average age of the patients with meningoencephalitis with parotitis (7.7 years) and of the patients without parotitis (7.0 years). Males constituted 19 (63 per cent) of the total number of cases.

The seasonal incidence of the cases in this series is presented in Fig 1. Cases were diagnosed in every season of the year, but the disease had its highest incidence in the spring and summer. Of interest is the fact that meningoencephalitis with parotitis was most frequent in the spring and meningoencephalitis without parotitis was most frequent in the summer.

The clinical manifestations of mumps meningoencephalitis are those characteristic of a widespread acute inflammation of the brain and of the meninges. These manifestations include symptoms and signs of encepha-

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*The performance of these tests is a public service available to all hospitals in Pennsylvania. During the period of this study, the laboratory was supervised by Dr. Werner Henle.

and convulsions, plus symptoms and signs of meningitis, i.e., stiff neck and spinal fluid pleocytosis. Table I indicates the most frequent symptoms and signs which occurred in these 30 cases of mumps meningoencephalitis together with the incidence of similar manifestations reported by Henle[13] and by Enders.[19]

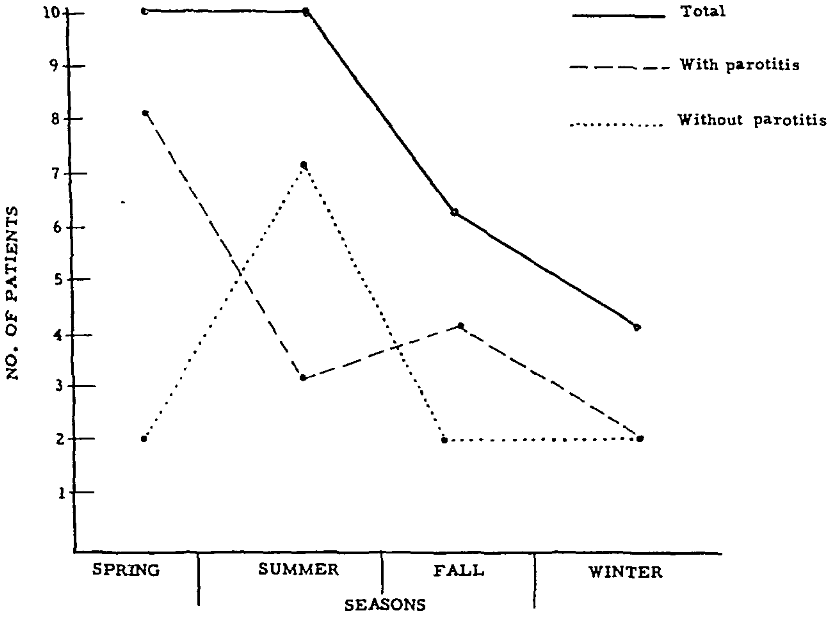

Fig. 1.—Seasonal incidence of mumps meningoencephalitis with and without parotitis.

Of the 30 cases of mumps meningoencephalitis, in 13 (43 per cent) there was no parotid, submaxillary, or sublingual swelling. The proof of infection by the mumps virus was made in these 13 cases by rising serologic titers against the mumps virus in paired sera from each patient. The other 17 patients (57 per cent) had parotitis at intervals ranging from 9 days before to 5 days following the appearance of the central nervous system manifestations. Three children were admitted with symptoms and signs of meningoencephalitis and their parotid swelling developed later in the course of the illness. These 3 cases plus the 13

TABLE I. SYMPTOMS AND SIGNS OF MUMPS MENINGOENCEPHALITIS (FIGURES STATED AS PERCENTAGE OF TOTAL GROUP)

SYMPTOMS AND SIGNS	PRESENT STUDY (30 CASES)	KANE AND ENDERS[19] AND HENLE ET AL.[13] (COMBINED TOTAL, 107 CASES)
Headache	66.6	59.9
Vomiting	73.3	65.8
Lethargy	50.0	26.7
Convulsions	10.0	13.0
Abdominal pain	13.8	20.7
Nuchal rigidity	63.6	62.4
Positive Kernig and/or Brudzinski	30.0	26.7

cases in which parotitis never occurred produced 16 cases (53 per cent) in which the etiologic diagnosis was not ascertainable at the time of hospital admission.

There were no cases of sublingual or submaxillary adenitis and no instances of orchitis in the 30 cases.

Abdominal pain was a persistent and severe complaint in 4 children. Serum amylase determinations were performed on sera from these 4 patients and 3 of them had elevated titers, i.e., 227, 326, and 560 units per 100 ml. of serum, respectively. (Normal value—50 to 150 units per 100 ml. of serum.) Since elevated serum amylase titers can occur with parotitis in the absence of pancreatitis, these 3 patients were considered on clinical grounds to have mumps pancreatitis. Each of these patients also had parotitis.

The severity of the illness varied. On admission, 2 of the children did not appear ill. One of these was admitted for investigation of falling spells, the other because of a questionably stiff neck in an afebrile child. The remaining children were categorized as follows: 7 were mildly ill, 17 were moderately ill, and 4 were severely ill. Two of the severely ill children had generalized convulsions.

Fever of 101° F. or higher rectally was present on admission in 26 of the 30 patients. Two of the remaining 4 patients gave a history of having had significant temperature elevations prior to admission but did not have fever on admission or subsequently during the hospital course. The total duration of fever above 101° F. rectally was from zero to 9 days, with an average of 5.3 days. By the time temperatures were below 100° F. rectally, the children appeared clinically well. No complications were observed during the course of illness in any of the cases.

A summary of the cerebrospinal fluid findings and peripheral blood cell counts will be found in Table II. There was no correlation between the height of the cerebrospinal fluid cell count and the severity of the illness. Repeat lumbar punctures were done if the clinical course was prolonged or seemed unusual. Pleocytosis in the spinal fluid persisted as long as 30 days after the onset of the meningoencephalitis.

The treatment was principally symptomatic and supportive. Rest, hydration, measures to control high fever and convulsions, and treatment of concurrent infections were used. Intravenous fluids were necessary for periods of 24 to 48 hours because of vomiting or dehydration in 19 of the children. Antibiotics were administered to 24 of the 30 patients until the

TABLE II. DATA ON CEREBROSPINAL FLUID AND BLOOD STUDIES IN 30 CASES OF MUMPS MENINGOENCEPHALITIS

COMPONENT	AVERAGE	RANGE	PER CENT OF CASES ABNORMAL	NORMAL VALUES
WBC in CSF (Cells/c.mm.)	357	15-1212	100	<10
Per cent lymphocytes in CSF	89	30-100*	—	—
Total protein in CSF (Mg./100 ml.)	48.5	17-140	50	<40
WBC in blood (1,000/c.mm.)	9.5	5.4-17	30	5-10
Per cent lymphocytes in blood	34	10-55	—	—

*Only one patient had less than 50 per cent lymphocytes in the CSF.

illness was established as being definitely nonbacterial in etiology. Coincidental bacterial infections were also treated with antibiotics as indicated. Complete bed rest was maintained during the hospitalization period in all cases and gradually increasing activity was permitted during convalescence at home. The average time of hospitalization for all cases was 9.1 days with a range of 5 to 19 days.

Demyelinating or leukoclastic encephalitides are produced as an expression of an allergic reaction by the nervous system during the course of some diseases in experimental animals and ACTH or corticosteroids have been used in preventing the development of some demyelinating encephalopathies under precise experimental conditions.[20, 21] Since it is possible that some cases of mumps meningoencephalitis in human beings are due to an allergic mechanism, adrenocorticotrophic hormone was given to 2 children in this study group. The therapy produced no measurable effect upon the clinical course of the disease.

Follow-up examinations were obtained on all children except one child who was killed in an accident prior to her return visit.

Sequellae appeared in one 6-year-old boy who developed staring spells 2 years after convalescence from mumps meningoencephalitis. The child had an abnormal electroencephalogram evidenced by biparietal and bifrontal spikes occurring in sleep. At the present time his symptoms are partially controlled with diphenylhydration and phenobarbital therapy.

SEROLOGIC STUDIES

Paired blood samples were drawn for serologic studies on 11 of the 17 cases of meningoencephalitis with parotitis and on all of the 13 cases of meningoencephalitis without parotitis. The data on the results of these titer studies are summarized in Tables III and IV.

The sera were tested in each case for complement fixing antibodies against mumps soluble antigen (S antigen), a small molecule attached to the membrane of the chick embryo on which the mumps virus is grown, and against mumps virus antigen (V antigen), a larger molecule attached to the virus particle itself.[13] The antibody titers are expressed as the highest initial dilution of serum which completely fixed complement in the presence of the mumps antigen. The first sera were obtained on an average of 3.5 days after the onset of the meningoencephalitis with a range of 2 to 5 days. The second sera were obtained on an average of 13.3 days after the first specimen was drawn with a range of 5 to 54 days.

It has been stated that a presumptive diagnosis of mumps infection can be made from one serum specimen provided that the mumps anti-S antibody titer is significantly greater than the mumps anti-V antibody titer.[13] Of the 13 meningoencephalitis patients without parotitis, 4 patients (Cases 20, 21, 22, 30) demonstrated a significantly higher* mumps anti-S antibody titer than the mumps anti-V antibody titer in the initial serum. Among the 3 cases in whom parotitis developed following the onset of the meningoencephalitis, one patient (Case 5) had a higher anti-S than anti-V titer in the initial sera. Thus, a total of $\frac{5}{16}$ patients (31.2 per cent) with meningoencephalitis without initial parotitis had

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*Defined as a fourfold difference in titer between the two antibodies.

TABLE III. COMPLEMENT FIXATION ANTIBODY TITERS IN 17 CASES OF MUMPS MENINGOENCEPHALITIS WITH PAROTITIS

CASE NO.	AGE (YEARS)	SEX	INITIAL SERUM			SECOND SERUM			TIME RELATIONSHIP OF PAROTITIS TO MENINGOENCEPHALITIS		
			ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	DAYS BEFORE DISEASE	ONSET WITH DISEASE	DAYS AFTER DISEASE
1	7	M	1:8	1:8	4	1:16	1:32	60		X	
2	6	M	1:8	1:2	2	1:16	1:32	15	4		
3	6	M	—	—	—	—	—	—	7		
4	11	F	—	—	—	—	—	—	1		
5	3	F	1:8	<1:2	3	1:32	1:64	13			4
6	7	M	—	—	—	—	—	—	1		
7	7	F	1:8	1:32	2	1:32	1:64	8	9		
8	11	F	1:64	1:128	5	1:64	1:512	15	3		
9	8	F	1:64	1:16	5	1:64	1:64	13		X	
10	6	M	—	—	—	—	—	—	3		
11	6	M	1:2	<1:2	2	1:16	<1:2	10			5
12	7	M	1:32	1:8	3	1:32	1:64	18	6		
13	11	F	—	—	—	—	—	—	7		
14	7	F	—	—	—	—	—	—	3		
15	9	M	1:64	1:256	4	1:64	1:256	22	9		
16	10	M	1:32	1:32	5	1:128	1:128	13	3		
17	9	M	1:16	1:16	5	>1:64	>1:64	35			4

*Anti-S titer means complement fixation antibody titer against mumps soluble antigen.

†Anti-V titer means complement fixation antibody titer against mumps virus antigen.

TABLE IV. COMPLEMENT FIXATION ANTIBODY TITERS IN 13 CASES OF MUMPS MENINGOENCEPHALITIS WITHOUT PAROTITIS

CASE NO.	AGE (YEARS)	SEX	INITIAL SERUM			SECOND SERUM		
			ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN	ANTI-S* TITER	ANTI-V† TITER	DAY OF DISEASE DRAWN
18	9	M	1:4	1:4	3	>1:64	1:64	20
19	11	M	1:8	1:4	2	1:32	1:32	20
20	3	M	1:32	1:4	5	1:32	1:64	13
21	6	F	1:4	<1:2	4	1:16	1:8	11
22	9	M	1:32	<1:2	3	1:32	1:4	10
23	3	M	1:8	1:8	3	1:32	1:128	8
24	6	M	1:8	1:32	2	1:32	>1:128	13
25	2	M	<1:2	<1:2	5	1:128	1:128	13
26	13	F	1:2	1:2	2	1:16	1:128	15
27	2	M	<1:2	1:2	3	1:32	1:32	18
28	7	M	1:64	1:32	4	>1:128	1:128	12
29	9	F	1:64	1:128	5	1:64	1:512	12
30	13	F	1:32	<1:8	2	1:64	1:32	17

*Anti-S titer means complement fixation antibody titer against mumps soluble antigen.
†Anti-V titer means complement fixation antibody titer against mumps virus antigen.

an antibody pattern in the first serum in which the anti-S antibody titer exceeded the anti-V antibody titer.

In the 8 cases in whom parotitis was present before the onset of, or occurred simultaneously with, meningoencephalitis 3 patients (38 per cent) demonstrated this presumptively diagnostic antibody pattern (anti-S greater than anti-V) in the initial serum. Thus, of the 24 children in whom serologic studies were done 8/24 (33.3 per cent) had a higher mumps antisoluble antibody titer than the mumps antivirus antibody titer in the first serum specimen.

All of the 24 patients except one (Case 15), who had parotitis, showed a fourfold or greater rise in the antibody titers against mumps soluble, mumps virus, or both mumps antigens when the second serum titer was compared with the first serum titer. Such an increment in serum titers is considered to be diagnostic of mumps infection.[13, 19]

During the same time interval which this study encompasses, 54 patients with nonbacterial meningoencephalitis in whom the etiological diagnosis was never established were admitted to the Pediatric Service and were studied. Paired serum specimens from 48 of these 54 patients were sent to the Virus Diagnostic Laboratory for analysis and all were reported negative for evidence of current or recent mumps infection. Since almost all patients infected with the mumps virus develop complement fixing antibodies against mumps antigens,[22] it seems reasonable to assume that few, if any, cases of mumps meningoencephalitis without parotitis were not diagnosed during the period of this study.

DISCUSSION

The exact incidence of meningoencephalitis as a complication of mumps infection is unknown. It has been estimated that in 40 per cent of all cases of mumps infection there is no clinical evidence of disease.[22, 23] The reported incidence of meningoencephalitis occurring in epidemics of mumps infection has varied from one to 65 per cent.[24] It is possible that any reported incidence of central nervous system involvement in mumps is misleading since mumps is principally a benign disease of childhood and only those cases with unusually severe symptoms or with complications are hospitalized and studied.

The predominance of meningoencephalitis with parotitis in the spring and the predominance of meningoencephalitis without parotitis in the summer was observed in this series and in series reported by Henle, Kilham, and Enders.[3, 13, 14, 19] The reason for this seasonal variation is uncertain but some facts are known which bear upon the problem. March and April are the months of highest incidence of clinical parotitis due to mumps[18] and of meningoencephalitis with parotitis. The experimental observations of Johnson and Goodpasture[25] and of Kilham[3] suggest that, in the summer, inapparent parotid infections with mumps virus may serve as the nidus for meningoencephalitis due to the same agent, but why mumps parotitis is frequently a subclinical infection in the summer and a clinical entity during other seasons of the year is still a mystery.

That mumps meningoencephalitis without parotitis is predominantly a disease of summer is of practical importance for it is during this same season that poliomyelitis in both the paralytic and nonparalytic forms occurs with greatest incidence.[14] This seasonal coincidence of nonparalytic poliomyelitis and mumps meningoencephalitis without parotitis makes the differential diagnosis of these similar clinical entities difficult without the use of ancillary diagnostic methods such as the mumps complement fixation test.

The clinical picture and course of our patients did not differ significantly from other reported series of mumps meningoencephalitis with the exception that no neurological complications were observed during the course of illness and sequellae developed in only one patient. There are reports in the literature of complications and sequellae occurring with mumps meningoencephalitis. These include death, optic neuritis, deafness, ocular palsy, hemiparesis, spasticity, isolated muscle weaknesses, quadriplegia, and personality changes.[1, 12, 14, 26] However, the incidence of such complications is low. Ford[27] states that the prognosis for complete recovery is excellent.

Serologic evidence of mumps infection is necessary to determine the etiology of mumps meningoencephalitis without parotitis in lieu of culturing the virus from the patient. Substantiating the etiology of a disease by serologic methods requires the demonstration of significant differences in antibody titers between two sera drawn from the patient, one early and one later in the disease. However, it has been shown that in 60 per cent of cases of subsequently proved mumps meningoencephalitis a presumptive diagnosis of mumps infection can be made from the antibody titers of the first serum sample, provided the anti-S antibody titer is significantly higher than the anti-V antibody titer.[13] This incidence of presumptive diagnosis from a single serum occurs only if the initial serum is drawn within the first week of clinical illness, for the incidence of a presumptively diagnostic serum pattern falls to 40 per cent if the initial serum is obtained after the first week of illness. If there is no significant difference between the antibody titers in paired sera, or if only one serum is obtained, an antibody titer of 1:32 or greater against either or both mumps antigens enables a diagnosis of recent mumps infection to be made.[13] However, on this basis alone there can be no certainty that the illness under investigation is due to mumps. Confirmation of the presumptive diagnosis requires a second serum showing a fourfold or greater rise in antibody titer against one or more antigens.[13, 19]

The data presented from our cases demonstrate the value of the presumptive single serum, double antigen, complement fixation test for diagnosing mumps meningoencephalitis. A diagnosis of mumps meningoencephalitis from the antibody pattern in a single serum was possible in 32 per cent ($\frac{5}{16}$) of patients with meningoencephalitis without initial parotitis, and subsequent serologic studies of paired sera proved the correctness of the original etiological diagnosis in all of the patients in whom the diagnosis was made. Thus, the presumptive diagnostic antibody titer pattern, when present, is valid evidence of the presence of mumps infection and is most useful for making a rapid etiological diagnosis in cases of mumps meningoencephalitis without parotitis.

SUMMARY

1. The epidemiology, clinical course, and serologic findings in 30 cases of mumps meningoencephalitis occurring in children under 14 years of age are presented.

2. Thirteen patients did not have parotitis at any time during the course of their meningoencephalitis. Of the remaining patients, 12 had parotitis prior to, 2 had parotitis concomitant with, and 3 had parotitis following the onset of symptoms of central nervous system involvement.

3. Fifty-five per cent of the cases of meningoencephalitis without parotitis occurred in the summer season. Forty-seven per cent of the cases of meningoencephalitis with parotitis occurred in the spring season.

4. A presumptive diagnosis of mumps infection was made in 32 per cent of the cases of mumps meningoencephalitis without parotitis on the basis of the presence of a higher mumps antisoluble antibody titer than the mumps antivirus antibody titer in the initial serum drawn within the first 5 days of illness.

5. Confirmation of the etiological diagnosis was possible in all of the 13 cases of mumps meningoencephalitis without parotitis and in 10 of the 11 serologically studied cases with parotitis by demonstrating a significant rise in the complement fixation antibody titer against mumps soluble or mumps virus antigen in a second serum drawn at least 5 days days after the first serum was obtained.

6. No complications were observed during the course of illness in any of the 30 cases. A convulsive disorder occurred in one patient 2 years after recovery from meningoencephalitis.

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IDIOPATHIC HYPERCHLOREMIC RENAL ACIDOSIS

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Two cases of idiopathic hyperchloremic acidosis are presented, one illustrating recovery following prompt recognition and treatment of the disease, and the other demonstrating irreparable renal damage when the nature of the illness was not recognized until the patient was 5½ years old. The salient biochemical abnormalities are shown, and the importance of early diagnosis and appropriate treatment is emphasized.

Case 1.—J. C. was first seen at the age of 5½ years. The parents and two siblings were living and well. The patient was thriving until she was 2 years of age when she experienced frequent episodes of pyuria. At the age of 4 years polydipsia and polyuria were noted. An intravenous pyelogram one year later demonstrated medullary renal calcifications and an otherwise normal urinary tract. Radiography of the bones was normal.

The available records show that at the age of 9 months the patient was well above the 50 percentile position for weight (9 kilograms) and length (71 cm.). Her physical development then began to fail. At 18 months she was at the 40 percentile (10.7 kilograms, 80 cm.), at 2½ years at the 25 percentile for weight (12.8 kilograms) and 15 percentile position for height (88 cm.), and at 5½ years of age below the 10 percentile position for weight (16 kilograms) and height (106) cm.).

At 5½ years she was physically well, of short and thin body build; the weight was 16 kilograms, the height 106 cm. The physical examination was normal. Laboratory data were: hemogram normal; Mantoux test negative; serum: carbon dioxide content 16.2 mEq. per liter, chloride 115 mEq. per liter, calcium 10.9 mg. per cent, phosphorus 3.94 mg. per cent, and alkaline phosphatase 18.7 Bodansky units. Urinalysis showed: pH (pHydrion paper method) on 4 fresh specimens, 6,7,7,7; albumin negative; sediment normal; maximal specific gravity on urinary concentration test 1.010. She voided 1,300 ml. in 24 hours; the pH of this specimen was 7.08 by electrometric measurement; the titratable acidity was 0.5 mEq., and the ammonia content 49.1 mEq. per 1.73 square meter per day.

The diagnosis of hyperchloremic renal acidosis with secondary renal calcifications was made and the patient was placed on a solution consisting of 200 Gm. sodium citrate, 100 Gm. citric acid, water to 1;000 ml., of which she received 40 ml. per day, providing 5 mEq. of sodium per kilogram per day. She was treated for three months during which time she was well and gained 1.8 kilograms. The serum carbon dioxide reached 18 mEq. per liter and the serum chloride was 108 mEq. per liter. Therapy then was discontinued for one month. During this time she lost 0.2 kilogram of weight, the serum carbon dioxide fell to 14.5 mEq. per liter, and the serum chloride rose to 118 mEq. per liter. In 24 hours

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she voided 950 ml., the urinary pH was 7.29 titratable acidity 1.2 mEq., and the ammonia content 21.2 mEq. per 1.73 square meters per day.

During the subsequent 10 months of therapy the serum carbon dioxide varied between 19 and 21 mEq. per liter, the serum chloride dropped to 105 mEq. per liter, the phosphorus was 4.5 mg. per cent, the nonprotein nitrogen was 28.2 mg. per cent, and the alkaline phosphatase dropped to 14.2 and later to 8.8 Bodansky units. There was a weight gain of 5 kilograms. The patient attained the 60 percentile position for weight (22.6 kilograms), and the 35 percentile position for height (117 cm.). She was feeling well.

CASE 2.—T. A. was admitted to Bellevue Hospital at the age of 8 weeks. Father, mother, and a 15-month-old sister were in good health. The patient was born after a normal pregnancy, the birth weight was 3.6 kilograms. He was fed a conventional milk, water, and carbohydrate mixture. Twenty drops of Vi-Penta had been added daily. Projectile vomiting shortly after the feeding had been present almost since birth. Two weeks prior to admission he also developed diarrhea. No medication was given.

On admission the patient weighed 2.4 kilograms, was severely dehydrated, showed muscular hypotonia, and was critically ill. The remainder of the physical examination was within normal limits.

Laboratory data were: hemoglobin 11.5 Gm. per cent, erythrocyte count 4.4 million, leukocyte count 19,000. Urinalysis showed: pH 6.0, albumin 1 plus, Sulkowitch test 1 to 2 plus, and a few white blood cells and hyaline casts in the sediment. The serum carbon dioxide content was 9 mEq. per liter, the chloride 121 mEq. per liter, the sodium 147.5 mEq. per liter, the potassium 4.45 mEq. per liter the nonprotein nitrogen 29.1 mg. per cent, the calcium 11.6 mg. per cent, the phosphorus 4.31 mg. per cent, and the total protein 8.15 Gm. per cent. A gastrointestinal series was normal; radiograms showed some osteoporosis and no evidence of nephrocalcinosis. A glucose tolerance test, a serum electrophoretic pattern, and the formaldehydogenic hormone excretion were normal. A two-dimensional paper chromatogram of a urine specimen showed a normal pattern of amino acids.

Hospital Course.—After correction of the dehydration with parenteral fluids, the patient was placed on an oral solution consisting of 100 Gm. of sodium citrate and 60 Gm. of citric acid in 1000 ml. This mixture was administered in a dose of 12 to 60 ml. per day, providing an average of 5 mEq. of sodium per kilogram per day until the patient reached 21 months of age. Alkali therapy was then discontinued. After a short period of acidosis and arrest of weight gain but no other clinical manifestations, the weight gain was resumed and the values for serum bicarbonate and serum chloride remained fairly stationary at normal levels. The weight at the age of 2 years was 11 kilograms.

During the first few weeks of hospitalization the following observations were made: (1) Discontinuance of citrate therapy resulted in arrest of weight gain, and reappearance of vomiting and acidosis. (2) Replacement of part of the sodium by potassium citrate did not change the muscular hypotonia, the serum potassium level, or the electrocardiogram. The patient became more acidotic. Potassium was therefore discontinued. (3) Treatment with monosodium-dihydrogen phosphate (400 mg. phosphorus daily) produced arrest of weight gain, humoral acidosis, a large increase in urinary phosphorus excretion, but no change in urine pH.

Throughout the observation of the patient it was noted that he was extremely susceptible to infections which were accompanied by extensive shifts in the water and electrolyte metabolism. The weight dropped immediately from minor infections, and parenteral fluids had to be used liberally to prevent or correct acidosis.

TABLE I

DATE	SERUM (mEq./L.)		THERAPY	URINE		
	CO_2	CL		pH	AMMONIA (mEq./1.73 m²/day)	TITRATABLE ACIDITY (mEq./1.73 m²/day)
2-15-51	9	121	Na citrate			
3- 5-51	21.6	110	Na Citrate			
3-16-51	16	114	None	6.2	78	16
3-19-51	18.4	110	None	6.2	45	13
3-21-51	22	110	None	6.2	63	15
3-28-51		118	None	6.7	19	7
4-13-51	18	109	None	6.1	45	19
4-19-51	19.8	107	None	7.1	32	7
4-25-51	21.8	102	NaH_2PO_4	6.3	35	40
5- 1-51	21.6	102	NaH_2PO_4	6.1	32	31
5- 7-51	20.7	108	NaH_2PO_4			
5-14-51	14.5	118	NaH_2PO_4	6.2	50	29
5-21-51	18.9	105	Na Citrate			
6-11-51	18	108	Na Citrate			
6-18-51	18	108	Na and K	7.2	8	24
6-25-51	15.3	118	Citrate			
7- 6-51	13.5	113	Citrate			
7-12-51	17.1	111	Na Citrate			
8-13-51	17	97	Na Citrate			
9- 4-51	20.4	104	Na Citrate	7.8	13	0
11-13-51	23.4	109	Na Citrate			
12- 9-51	20.3	100	Na Citrate			
2-18-52	20.7	107	Na Citrate	8.2	0	0
2-21-52	17.1	111	None			
2-25-52	15.7	130	None	5.8	45	47
2-29-52	17.5	108	Na Citrate			
3-27-52	18.9	118	Na Citrate			
5-27-52	19.8	109	Na Citrate			
7-24-52	22.5	104	Na Citrate			
9- 4-52	20.7	112	Na Citrate			
10- 6-52	17.1	110	None			
10-11-52	16.2	113	None			
10-17-52	15.3	115	None			
10-24-52	20.7	112	None			
10-31-52	20.7	112	None			
12-10-52	18.9	114	None	6.7	37	11
1- 7-53	19.3	109	None	6.2	54	26

The most consistently abnormal laboratory finding was a low titratable acidity and ammonia excretion in the urine, accompanied by a relatively high urinary pH (Table I, Fig. 1).

DISCUSSION

Clinical Aspects.—

Natural course: Idiopathic hyperchloremic renal acidosis is caused by a renal tubular defect of conservation of fixed base, resulting in a metabolic acidosis and excretion of urine of a higher pH than expected in the presence of metabolic acidosis. It begins at or shortly after birth. The severity of symptoms depends on the degree of the defect. In severe cases the diagnosis is established in infancy after chemical investigation of failure to thrive, muscular hypotonia, constipation, anorexia or vomiting.[1-19] Without proper therapy, the disease results in death from dehydration and acidosis or intercurrent infection. If it is treated properly for weeks or months, spontaneous recovery seems to ensue. Patients with a mild form of this disease are apt to be overlooked in infancy and the diagnosis is made only in later childhood or adult life,[20-31] after renal deposition of calcium has caused secondary damage to the distal tubules and demineralization of the skeleton. Polydipsia and polyuria or a renal stone may be the first symptoms; or an intravenous pyelogram, because of repeated urinary infections, may show nephrocalcinosis; or radiography of the bones may demonstrate changes secondary to chronic acidosis (osteoporosis, osteomalacia, late rickets).

Diagnosis: The diagnosis of hyperchloremic renal acidosis may be suspected when the kidneys fail to produce a urine as acid as that observed in comparable "normal" infants when they are placed under the stress of a comparable degree of metabolic acidosis, and when other renal disorders have been eliminated by urine culture, intravenous pyelography, etc.

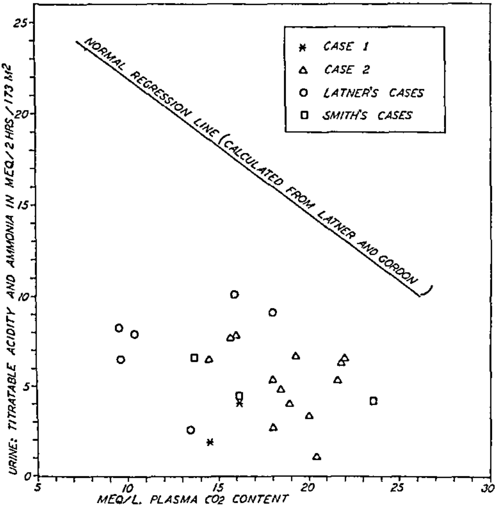

Fig. 1.—Deficiency of renal base economy. Values fall below normal regression line.

Differential diagnosis: Table II lists the clinical differential diagnostic considerations and the principal feature in their distinction from idiopathic hyperchloremic renal acidosis.

In the differential diagnosis of the biochemical abnormality of hyperchloremia, lowered plasma carbon dioxide, and relatively high urinary pH, consideration must be given to abnormal

TABLE II. DIFFERENTIAL DIAGNOSIS OF IDIOPATHIC HYPERCHLOREMIC RENAL ACIDOSIS

DISEASES	DIFFERENTIATING CRITERIA
Improper feeding technique:	
Vitamin D intoxication	History, chemical investigation
Underfeeding:	
Deficiency in calories, protein, or vitamins	History
Anomalies of gastrointestinal tract:	
Esophageal or pyloric anomalies	Radiography
Congenital megacolon	Radiography
Intermittent volvulus	Radiography
Malrotation of intestine	Radiography
Renal diseases:	
Congenital anomalies	Radiography
Infections	Urinalysis
Renal diabetes insipidus	Chemical and hormone investigation
Central nervous system disturbances:	
Brain injury	History
Subdural effusion	Subdural taps
Endocrine disturbances:	
Hypothyroidism	Chemical and hormone investigation
Hypoadrenalism	Chemical and hormone investigation
Hyperparathyroidism	Chemical and hormone investigation
Metabolic diseases:	
Fanconi syndrome	Chemical investigation
Idiopathic hypercalcemia	Chemical investigation
Hypophosphatasia	Chemical investigation

oral intake, such as calcium chloride, or abnormal losses from the gastrointestinal or urinary tract. The first two of these conditions are usually easily detected, but impairment of the renal function due to congenital anomalies or infections should be diagnosed by appropriate laboratory studies, such as urine culture, intravenous pyelography, blood urea nitrogen determination, etc. Hyperventilation due to injury of the central nervous system or poisoning may produce hyperchloremia and lowered plasma carbon dioxide with a urine in the alkaline or slightly acid range. The serum pH, however, will be elevated.

Prognosis: The prognosis depends on the extent of irreversible renal damage and the proper management. The ultimate prognosis often is better in the more severely affected cases, because they are diagnosed early and treatment is begun before irreparable changes have been established.

Treatment: The aim of therapy is to correct the acidosis in order to prevent further mobilization, renal filtration, and distal tubular deposition of calcium and to replace the continued urinary loss of fixed base. This can be achieved by administration of alkali. A 10 per cent sodium citrate with 6 per cent citric acid solution is more commonly used than bicarbonate or lactate. The amount of alkali and the duration of therapy vary with every patient. Normal weight gain and almost complete correction of the acidosis should be achieved. The need for alkali often changes spontaneously, especially in infants, but always increases in the event of intercurrent infection, a common occurrence in these subjects.

Biochemical Aspects.—In the normal infant and child, and in most adults, diet, growth, metabolism, and intestinal excretion make it necessary for the kidneys to excrete more chloride, phosphate, sulfate, and organic acids than sodium, potassium, calcium, and magnesium, if the composition of the body fluids is to be maintained. Two mechanisms are provided by the renal tubular cells to accomplish this purpose. Both of these mechanisms, the hydrogen ion exchange mechanism and ammonium production, are interrelated. The conservation of base in the urine may be expressed as titratable acidity plus ammonium minus bicarbonate in the urine.[32] In the cases just presented we believe that there is, for an unknown reason, a diminished ability of the renal tubular cells to furnish hydrogen ions in exchange for sodium, potassium, calcium, and magnesium and to permit any large production of ammonium ions. Latner and Burnard[11] have postulated a primary defect of reabsorption of bicarbonate in the proximal renal tubule. This view has been challenged by Smith and Schreiner.[31] At present the exact mechanism is still unknown. This defect in the conservation of basic minerals by the renal tubules can be demonstrated graphically by plotting the sum of the major factors in base conservation (titratable acidity and ammonium) in the urine against the plasma carbon dioxide content (Fig. 1). The regression line, obtained from data for normal and even young premature infants,[11, 33] indicates that as the plasma carbon dioxide falls in a metabolic acidosis, the amount of base conservation per unit of time and per unit of surface area should increase. As seen in Fig. 1, the determinations for Latner's,[11] Smith's,[31] and our patients all fall below the line showing the insufficient production of hydrogen ions and ammonia.

SUMMARY

Two cases of idiopathic hyperchloremic renal acidosis are presented. One was diagnosed when the patient was 8 weeks of age by chemical investigation of persistent acidosis. Appropriate treatment, consisting of the addition of sodium citrate to his dietary intake for 20 months, resulted in apparently complete recovery. The other case was diagnosed when the child was 5½ years of age, when renal calcifications were radiographically visualized. Continued alkali therapy corrected the acidosis and had a favorable effect on the physical development of this patient.

The natural course of this disease is presented. The disturbance of the electrolyte metabolism is described, with emphasis on its importance in early detection of this disease and on the elimination of other illnesses which clinically may simulate this condition.

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PSEUDOTUMOR CEREBRI

BENIGN INTRACRANIAL HYPERTENSION

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PSEUDOTUMOR CEREBRI is a syndrome characterized by (1) increased intracranial pressure, (2) a normal ventricular system, and (3) a normal spinal fluid except for pressure. Its clinical features resemble those of an intracranial space-occupying mass, but no mass can be demonstrated by ventriculography, encephalography, arteriography, or surgical exploration.

The purpose of this paper is to present 6 cases of this syndrome occurring in children and to discuss the etiology, symptomatology, treatment, and prognosis.

REVIEW OF LITERATURE

Pseudotumor cerebri was clearly defined as a precise syndrome by Davidoff and Dyke[1] and Dandy,[2] based on the cardinal radiologic feature of a normal ventricular system under increased pressure. It had previously been referred to in the literature as serous meningitis,[1, 2, 5, 6] pseudoabscess,[3] otitic hydrocephalus,[4] or intracranial pressure without brain tumor.[2, 5, 8]

Many authors have attempted to implicate dural sinus thrombosis as the main etiological cause of this syndrome.[4, 9] Ray and associates[10] initially supported this thesis using dural sinusography as a diagnostic technique. However, reporting on 28 cases at the Harvey Cushing Society in 1955, Ray was able to demonstrate evidence of thrombosis in only 10 of the 20 sinograms. He concluded that there were obviously a high percentage of cases in which dural sinus thrombosis could not be held responsible.

Foley[12] gathered 106 cases from the literature and reviewed 60 cases at his own hospital. He suggested that the term "benign intracranial hypertension" be used to describe those cases of pseudotumor cerebri in whom no antecedent trauma, infection, or dural sinus thrombosis is found.

Except for the recent article by Moore,[13] there has been scant reporting in the pediatric journals. This may be partially explained by the fact that this syndrome occurs most frequently in the second and fourth decade of life.

CASE REPORTS

CASE 1.—B. F., a 6½-year-old white boy, was admitted to Mount Sinai Hospital in New York City on Nov. 29, 1954, because of headache, ataxia, and vomiting. Some clumsiness and incoordination were noted during the 6 weeks prior to admission. These symptoms had become considerably worse 2 days prior to admission. He was unable to sit in a chair unsupported, began vomiting, and complained of headache.

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[*] From [illegible] The Long [illegible] Park, New [illegible] New York [illegible] lyn, N. Y.

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Physical examination revealed a well-developed, well-nourished, alert lad, in no acute distress. Blood pressure was 110/70 mm. Hg. Respiration, pulse, and temperature were normal. There was a moderate degree of generalized hypotonia and weakness. The deep tendon reflexes were normal. There were no pathologic reflexes. He demonstrated an unsteady, staggering gait and past pointing with the upper extremities. The examination of both fundi were normal, although several observers felt that some papilledema was present.

The neuroskull roentgenograms, electroencephalogram, pneumoencephalogram, and ventriculogram were normal. A red and white blood cell count, urine analysis, and complement fixation tests for mumps, eastern equine encephalitis, and Japanese type B encephalitis were normal. The spinal fluid examination was normal.

Bilateral frontal burr holes were made under general anesthesia. On the left side the brain came right to the dura. On the right side a good deal of subarachnoid fluid was present, which emptied forcefully through the incision.

The patient was discharged 6 days after admission. The headache and vomiting stopped and the weakness and ataxia decreased. It should be emphasized that throughout the entire illness he was never uncomfortable or in any acute distress.

The patient developed bilateral epidemic parotitis one day after discharge. This subsided without complication. Two weeks after discharge he was asymptomatic and had a normal physical and neurological examination. He is currently in good health and shows no neurological sequelae.

Case 2.—R. R., a 10-year-old white girl, was admitted to the Long Island Jewish Hospital, New Hyde Park, New York, on March 12, 1955, because of a suspected intracranial space-occupying mass following trauma. Ten days prior to admission the patient had fallen down a flight of stairs and traumatized the right side of her head. She had been dazed but not unconscious and began to vomit approximately one hour after her injury. She vomited often during the next 2 to 3 days and complained of vertigo. Following the accident she became irritable, apathetic, and complained of recurrent dizziness and headaches. On the day of admission she was quite alert and did not vomit. She complained of pain in the left ear. There was no history of any recent infection or illness.

Physical examination revealed a very cooperative, alert girl. Her temperature, pulse, and respiration were normal and her blood pressure was 120/70 mm. Hg. There was a large fluctuant subcuticular swelling in the right temporoparietal region of the skull. Slight nuchal resistance was present and there was a questionably positive Kernig sign. There were no gross weaknesses. The deep tendon reflexes were more active in the lower limbs than in the upper. No abnormal reflexes were present. The right pupil was slightly larger than the left but reacted equally to light and accommodation. There were slight nystagmoid jerks on extreme lateral gaze which were unsustained. Bilateral papilledema was present and fresh hemorrhages were noted at the periphery of the discs. The veins were engorged.

A total white and red cell count, urine analysis, Schick and Mantoux tests, and skull x-rays were normal. Several pre- and postoperative lumbar punctures yielded normal spinal fluid which was sterile. At the first lumbar puncture, spinal fluid pressure was 500 mm. of water. The spinal fluid pressure subsequently became lowered to 160 mm. of water.

Because of recurrent intermittent drowsiness, bilateral burr holes were placed 24 hours after admission. This disclosed an excessive accumulation of clear colorless spinal fluid in the subarachnoid space over both hemispheres. There was no evidence of a subdural hematoma. The postoperative course was uneventful and the papilledema and hemorrhages were noted to recede.

She was discharged from the hospital March 25, 1955, considerably improved and has remained in good health.

Case 3.—S. F., a 5½-year-old white boy, was admitted to the Long Island Jewish Hospital on Jan. 22, 1956, because of a casual observation of bilateral papilledema during a routine preschool examination. He had complained intermittently of headaches for 6 months prior to this examination. There had been no vomiting or loss of appetite.

The physical and neurological examinations were completely normal except for the eye findings. The optic discs showed bilateral papilledema in relatively early stages with some exudate but no hemorrhages. Routine studies, including skull roentgenograms and electroencephalograms, were normal. Spinal fluid analysis was normal.

Burr holes were placed in preparation for a ventriculogram. The brain appeared to be under some tension. When the dura was opened an excessive amount of spinal fluid spurted out of the subarachnoid space. It was not possible to tap the right ventricle. However, air was easily injected into the left ventricle and a normal but small ventricular system was outlined. A right myoplastic type of decompression was done at this time, and the postoperative course was uneventful. At lumbar puncture, 4 days following the operation, an initial spinal fluid pressure of 90 mm. of water was found.

One month following admission he was asymptomatic and the eye grounds improved. His behavior was said to have become more relaxed, outgoing, playful, and aggressive. The patient acquired chicken pox in May, 1956. During this time he complained of severe headaches and a bulge was noted at the site of the operation. Five months postoperatively, papilledema disappeared from the right eye and was noted to be diminished in the left.

Case 4.—M. D., an 8-year-old white girl, was admitted to the Long Island Jewish Hospital on Nov. 16, 1956, because of loss of vision in her left eye of 1½ weeks' duration. Four weeks prior to admission the patient reported an incidental fall, at which time she had struck her head. She had no headache, nausea, loss of appetite, or vomiting.

The physical and neurological condition was normal except for the eyes. Vision in the left eye was 20/200. A 5 degree central scotoma and an enlarged blind spot were noted. There was papilledema obscuring the entire left disc. The macula was obscured by exudates. The vision in her right eye was 20/70. The blind spot was enlarged and the nasal margin of the optic disc was raised.

Following admission, bilateral burr holes were made. When the dura was opened the brain bulged and was under increased pressure. There were repeated unsuccessful attempts to tap each ventricle. A right-sided cerebral angiography was therefore carried out. Both anteroposterior and lateral views were normal. A lumbar puncture, which was then performed, revealed an initial pressure of 350-400 mm. of water. Pneumo-encephalogram, spinal fluid culture and analysis were normal. The skull x-rays were normal. A right-sided myoplastic decompression was done on Nov. 12, 1956. The child did well postoperatively. On the fifth postoperative day, spinal fluid pressure was found to be 170 mm. The fluid was slightly xanthochromic. The spinal fluid analysis was normal, except for a protein of 56 mg. The xanthochromia and elevated spinal fluid protein may have resulted from unsuccessful ventricular taps.

Normal spinal fluid pressure was recorded on the eleventh postoperative day. Two weeks following the operation, the child stated that her sight had improved. Neurological examination was negative and the area of decompression was soft and pulsating. Considerably less swelling and edema about the macula was noted. The electroencephalogram pre- and postoperatively showed diffuse cerebral dysrhythmia. The patient is currently asymptomatic and shows no abnormal eye findings.

Case 5.—R. F., a 10-year-old white girl, was admitted to the Long Island College Hospital in Brooklyn, N. Y., on July 22, 1952, because of severe headaches, and diplopia of 2 weeks' duration. Blood streaked stools were noted on the day prior to admission.

Physical examination revealed a well-developed, well-nourished girl in no acute distress. Her temperature, pulse, and respiration were normal. Blood pressure was 120/94 mm. Hg. A soft round liver edge was palpable 3 cm. below the costal margin. The tip of the spleen was also palpable. Paresis of the right external rectus muscle was apparent. There were scattered hemorrhages in the periphery of the left fundus, and moderate bilateral papilledema.

The white and red cell counts, erthrocyte sedimentation rate, urine analysis, nose and throat culture, Schick and Mantoux tests (0.1 mg. OT), and spinal fluid analysis were normal. Blood, urea, fasting blood sugar, total serum protein, albumin and globulin, cholesterol and esters and cephalin flocculation tests were normal. The serum bilirubin was 0.63 mg. per cent, alkaline phosphatase was 16 Bodansky units, and Bromsulfalein retention 11 per cent at 45 minutes. Biopsy of the liver showed hemorrhages and fibrosis compatible with subacute yellow atrophy. The electroencephalogram was characterized by diffuse slow activity, 6-8 cycles per second. Roentgenograms of the skull, chest, and abdomen were negative. Spinal fluid analysis was normal.

Except for an occasional mild headache and nausea the patient was generally asymptomatic and in good spirits. The papilledema, however, became more intense and there was a gradual loss of vision. Following a normal ventriculogram, a subtemporal decompression was carried out to protect her vision.

During the weeks that followed, the papilledema subsided, her vision was regained, and the headaches and diplopia disappeared. Six weeks after admission no abnormalities were noted on neurological examination. The patient, however, later developed cirrhosis of the liver and subsequently required splenectomy and a shunt operation.

Case 6.—S. F., a 6-year-old white boy, was seen 6 weeks following a normal routine examination because of headaches and fatigue of 3 weeks' duration. He was admitted to St. Joseph's Hospital, Far Rockaway, New York, and subsequently transferred to the Neurosurgery Service at the Long Island Jewish Hospital, New Hyde Park, on Jan. 15, 1955.

Partial paresis of both lateral rectus muscles was noted. There was moderate bilateral papilledema. Peripheral visual fields were normal. Laboratory studies including total white and red cell counts, urine analysis, serology test for syphilis, and spinal fluid analysis were normal. X-rays of the skull and chest were normal. The electroencephalogram showed diffuse slow activity. The signs and symptoms were suggestive of an unlocalized brain tumor. However, a diagnosis of chronic serous meningitis was considered more likely and the patient was referred home for observation.

He was readmitted to the hospital 10 days later, on Jan. 25, 1955, because of 4+ papilledema and complete paralysis of the right lateral rectus muscle. Roentgenograms of the skull at this time revealed slight separation of the occipital suture lines. The electroencephalogram again revealed diffuse slow activity. On Feb. 1, 1955, a normal ventriculogram was obtained. During the following 2 weeks, the papilledema was noted to recede and the paresis of the right rectus muscle improved. On May 24, 1955, no abnormalities were found on neurological and ophthalmological examinations. The patient has now been observed for 2 years and has remained symptom free.

intracranial pressure. Case 3 was, in fact, detected during a routine preschool physical examination.

Laboratory Tests.—Complete blood counts, urine analyses, and the viral complement fixation studies in Case 1 were normal. Spinal fluid characteristics were normal except for pressure. Skull x-rays were all normal except in Case 6 where some suture separation was noted. Ventriculograms were normal and the ventricles were often described as appearing somewhat smaller than usual.

TABLE I

			SYMPTOMS							CLINICAL SIGNS					MISCELLANEOUS				
PATIENT	AGE (YR.)	SEX	HEADACHE	VOMITING	DIPLOPIA	LOSS OF VISION	WEAKNESS	DIZZINESS	DROWSINESS	OCULAR PALSY	PAPILLEDEMA	RETINAL HEMORRHAGE	ATAXIA	INCREASED INTRACRANIAL PRESSURE	ABNORMAL EEG	SUTURE SEPARATION	ANTECEDENT TRAUMA	DURATION OF SYMPTOMS	PERIOD OF OBSERVATION (YEARS)
No. 1	6½	M	x	x			x				±		x	x				9 wk.	2½
No. 2	10	F	x	x				x	x		x	x		x			x	3 wk.	2
No. 3	5½	M	x					x			x			x				5½ mo.	1½
No. 4	8	F				x					x			x	x		x	6 wk.	1½
No. 5	10	F	x		x	x				x	x	x		x	x			8 wk.	5
No. 6	6	M	x				x			x	x	x		x	x	x		4 wk.	2½

COMMENT

Symptoms and Clinical Signs.—Headache of varying intensity occurred in 5 cases and was the most frequent symptom. Vomiting, diplopia, loss of vision, dizziness, drowsiness, and weakness occurred less frequently. Unilateral or bilateral papilledema was present in 5 cases; retinal hemorrhages were present in 3 cases, and ocular palsy in 2. One patient had ataxia.

The most impressive clinical feature of this syndrome, in children, has been their general well-being throughout the disease, in spite of the increased

Treatment.—The treatment for this syndrome is symptomatic, depending principally on the intensity of the disease. Some patients required subtemporal decompression for relief of headaches and, in others, it was necessary to prevent blindness.

DISCUSSION

The etiological agents of pseudotumor cerebri appear to be as diverse as they are numerous. Foley[12] classifies this syndrome into three main groups: (1) otitic cases in which dural sinus thrombosis is the probable cause of increased pressure; (2) a larger group in which there is no history of infection or injury, occurring almost exclusively in women, with a peak incidence in the fourth decade; and (3) a smaller group in which the condition follows an infection or mild head injury.

Effective use of antibiotics should prevent the extension of infection from the middle ear or mastoid area to the dural sinuses. One would therefore expect to find that more patients in the pediatric age group would fall into Group 2 and fewer into Group 3.

Cases 1 and 5 had illnesses which may have been coincident or associated with this syndrome. Case 1 developed mumps during his recovery period. His complement fixation test for mumps was negative during his hospital stay. Case 3 showed microscopic, pathologic, and biochemical evidence of subacute yellow atrophy. The onset of symptoms in Cases 2 and 4 followed a head injury.

Foley's report indicates that a slight pleocytosis is not uncommon. However, repeated spinal fluid analysis on our cases failed to show any indication of acute or chronic inflammatory or neoplastic disease.

The most common causes of increased intracranial pressure are: obstruction to the normal circulation or absorption of cerebrospinal fluid, a space-occupying mass, cerebral edema, and right ventricular failure. These may be differentiated with specific medical and neurosurgical diagnostic techniques.

It is difficult, however, to describe a mechanism which can explain the presence of increased intracranial pressure with an undistorted ventricular system. There is evidence that the increased pressure is due to an intracerebral collection of fluid. At operation, the brain tissue appears wet and swollen. It recedes rapidly as the fluid spurts out of the subarachnoid space.

Blindness may appear much earlier in this condition than in those due to cerebral tumor. This may be related to a sudden increased intracerebral pressure.

The diagnosis of pseudotumor cerebri is one made by exclusion. Careful studies and prolonged follow-up observations are necessary to exclude conditions which may pursue a chronic or recurrent course, such as subdural hematomas in unusual locations, subdural cysts, or ependymal tumors.

The prognosis for this disease is excellent. All of our patients recovered without any temporary or permanent sequellae. Zuidema and Cohen[8] noted, in their 20-year follow-up of cases in adults, that after 2 years it was unlikely for a tumor to arise from one of the silent areas of the brain.

SUMMARY

Six cases of pseudotumor cerebri are reported in children. The syndrome is characterized by headache, vomiting, papilledema, and unexplained increased intracranial pressure. The benign nature of this disease is emphasized.

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PEDICULOSIS CAPITIS IN PRESCHOOL AND SCHOOL CHILDREN: CONTROL WITH A SHAMPOO CONTAINING GAMMA BENZENE HEXACHLORIDE

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THE prevalence of pediculosis capitis remains a constant and troublesome problem in most communities, particularly among school children. Kaiser[1] noted that in Rochester, New York, it was the second largest cause of absenteeism during the 1944-1945 school year. Other surveys have found its prevalence among school children to range from less than 1 per cent to over 50 per cent.[2, 3]

Unlike the communicable diseases, the host does not develop an immunity to the ectoparasitic infestations and therefore the spread of pediculosis is not interrupted by the development of immunity in affected individuals. Hence, its control depends solely on enforcement of good hygienic practices and effective measures to rid infested individuals of the parasite.

Measures for eliminating pediculosis infestations should quickly destroy both lice and nits. Ideally, it should also be cosmetically acceptable and simple and safe to use. With such a pediculicide, supervisory problems would be minimized and the success of the program greatly enhanced.

The preparations that are presently available for the eradication of pediculi have several disadvantages. These lessen their acceptability and detract from the success of a control or eradication program. These disadvantages include: a required contact of up to 24 hours or more of the pediculicide to ensure effectiveness, a turbaned towel or other head covering during the medication contact period which can be embarrassing to the patient, unpleasant odors and other cosmetic inelegance and, with many preparations, a chance of skin irritation or sensitization.

Recently, a preparation was presented to us that offered the prospect of overcoming these disadvantages. This is a shampoo containing, as the active agent, gamma benzene hexachloride, a potent pediculicide and scabicide. In this shampoo,* the gamma benzene hexachloride is solubilized and combined with surface active agents. In vitro studies had demonstrated the shampoo to be capable of destroying nits within a few minutes, presumably because the surface active agent facilitated penetration of the pediculi and their ova.[4]

MATERIAL AND METHOD

Observations were made on 47 children, representing the number found affected during routine examinations of selected groups of children both by the school nurse and our Public Health Nursing Staff. No Negro patients were included in this group. Of the infested patients, 87.2 per cent were female.

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*Kwell Shampoo, kindly supplied by Reed & Carnrick, Jersey City, N. J.

Treatment was applied either by the nurse or by the parent of the child according to the following simple instructions: (1) thoroughly wet the hair with warm water, (2) apply the Kwell Shampoo as with any ordinary shampoo, (3) rub lather in vigorously for a full 4 minutes, being sure to go over the entire hairy area, (4) rinse hair thoroughly, (5) rub vigorously with a dry towel, and (6) if any nit shells remain, remove with a fine tooth comb. The following day, the children returned for re-examination.

RESULTS

In all cases, a single shampooing with the preparation proved effective in completely destroying all evidence of infestation. No live pediculi or nits were observed upon re-examination of these patients one to five days after treatment.

From Table I it can be seen that the shampoo was used in a total of 47 cases with an age distribution of 1 to 49 years. There were 41 cases of scalp infestation alone, 1 case of infestation of scalp and eyelashes, and 5 cases of pubic infestations. In all these cases, all evidence of live pediculi was eliminated after the first treatment. Additional applications of the shampoo were necessary in 8 cases to aid in the removal of residual nit shells. These might have been avoided with more vigorous shampooing technique. In Table II, we have shown the number of patients who have been shampooed one or more times. Of the total group, 39, or 83 per cent, were completely clear after one visit, 5 required a second treatment for removal of nit shells, and 3 required a second and third visit. In all, this represents a total of 58 separate applications.

TABLE II. PATIENTS SHAMPOOED ONE OR MORE TIMES

	NUMBER	PER CENT
One visit	39	83.0
Two visits	5	10.6
Three visits	3	6.4
Total	47	100.0

A noteworthy feature of treatment was the ready acceptance of the procedure, which is no different from a conventional hair shampooing. Both the mothers and nurses found the treatment pleasant and easy to use. No evidence of irritation or other adverse effect was encountered.

TABLE I. AGE DISTRIBUTION AND SITE OF INFESTATIONS

AGE GROUP	TOTAL	SCALP ONLY	SCALP AND EYELASH	PUBIC	PER CENT
1- 4	10	10			21.3
5- 9	15	15			31.9
10-14	5	5			10.6
15-19	8	4	1	3	17.0
20-24	6	5		1	12.8
25-29	1			1	2.1
30-34					
35-39	1	1			2.1
40-44					
45-49	1	1			2.1

DISCUSSION

A treatment for pediculosis that combines "one-shot" effectiveness with a high degree of patient-acceptance affords an opportunity for control of infestation at both the school and family levels. An advantage of the shampoo method of treatment is its simplicity and acceptability to patient and family. The method avoids the onus of previously available treatments that stigmatize the patient.

In Kwell Shampoo, the gamma benzene hexachloride is available in solution form rather than the previously available suspensions. In solution it apparently is much more rapidly effective in its pediculicidal action. In addition, the surfactant not only promotes penetration of the active agent into the parasite, but it also loosens nits from their attachments to the hair. Since safety is also an essential requisite for an acceptable pediculicide it is important to note that gamma benzene hexachloride has demonstrated a remarkable absence of toxic, irritative, or sensitizing effects.[6, 7]

SUMMARY

Forty-seven children affected with pediculosis capitis were treated with a shampoo containing 1 per cent gamma benzene hexachloride.

A single shampooing sufficed to eradicate infestation with pediculi and viable nits in all cases. The effect was achieved in a few minutes, the actual contact period of about 4 minutes and the total procedure taking no more time than an average shampoo.

Nurses and parents who administered the treatment reported it was both simple and pleasant to use, and readily accepted by the patient.

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SUPPURATIVE ORCHITIS DUE TO PSEUDOMONAS AERUGINOSA

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THE organism of "blue pus" is the only member of the group Pseudomonas which is pathogenic to man. The others form pigments of various colors and are widely distributed in soil and water. Wilson and Miles[5] summarize the pathogenic effects as follows: ". . . gives rise occasionally to suppurative processes and occasionally to generalised infection. Among the commonest manifestations are middle ear suppuration in children, destructive lesions of the skin, sometimes described as ecthyma gangrenosum, in children and adults, and necrotic and ulcerative lesions of the alimentary mucosa. The respiratory tract, the eye, the joints and the kidneys are sometimes affected. Wounds are often infected. There is also reason to believe that the organism plays a part in some cases of infantile diarrhoea. Infection may be primary or secondary and is often acute and rapidly fatal."

CASE REPORT

A boy, prematurely born and with a birth weight of 5 pounds 1 ounce, was slow to take food and on the tenth day, when his weight had dropped to 4 pounds 7 ounces, began to vomit. A tense tender swelling was found in the right groin. No testicle was felt in the right side of the scrotum. A tentative diagnosis of an obstructed inguinal hernia was made and operation was carried out under nitrous oxide and oxygen anesthesia, reinforced by a local anesthetic. The right inguinal canal was opened and a swollen and engorged testicle was found. No torsion could be demonstrated. The peritoneum was opened at the internal ring. The bowel observed was normal but a small quantity of blood-stained viscid fluid oozed out. The testis and cord were excised.

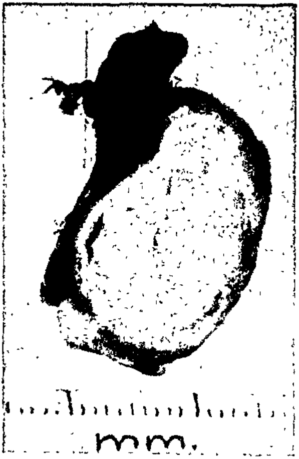

Fig. 1.—The abscess is seen to the left and the body of the testis to the right.

Two days after operation the child had a brief attack of diarrhea and recovered spontaneously in about 24

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hours. Otherwise convalescence was uneventful.

Pathology and Bacteriology.—The cut surface of the body of the testis showed a crescent-shaped zone of bluish green pus lying posteriorly and extending to both poles, its center being 1 cm. thick. In its concavity lay the body of the testis, lobulated on its posterior margin, the line of junction showing a thin zone of hemorrhage.

Histological section showed the purulent zone to be a solid mass of polymorphonuclear leukocytes. The body of the testis showed tubules in the embryonic state with occasional patency. The hemorrhagic zone was partly of fibrin in contact with the pus and partly of granulation tissue in contact with the tubules. The abscess was completely within the tunica albuginea.

Cultures from the viscid peritoneal fluid and from the abscess each gave a pure growth of *Ps. aeruginosa.* Culture of the stools during the bout of diarrhea gave a predominant growth of the same organism.

DISCUSSION

With the assistance of the librarian of a large reference library, we have been able to discover only one similar case in the literature. Longhi[3] describes a boy of 12 years of age who was admitted to a hospital with a history of testicular swelling for 4 weeks. When examined the swelling was the size of a hen's egg and adhered to the scrotal wall. No distinction could be made between the epididymis and the testis. The patient was in high fever and suffering great pain. There was no urethral discharge and no involvement of the prostate or vesiculae.

Treatment with penicillin was ineffective. The scrotal skin reddened and broke down extruding a fungating mass. Cultures of the initial discharge gave a pure growth of *Ps. aeruginosa.* Pain steadily diminished. Bismuth salicylate was then employed without effect and then streptomycin; finally sulfadiazine was given for a month. Meantime the mass steadily diminished to form a dense scar.

Wassermann and Kahn reactions were negative. Films of the discharge were negative for tubercle bacillus and guinea pig inoculation of the discharge gave no reaction. Dark ground examination of the discharge showed no treponemata and films of the urethral secretion and discharged showed no gonococci. *Ps. aeruginosa* was recovered repeatedly from the discharge and also from the urine.

Agglutination reactions between the patient's serum and suspensions of the infecting organism showed agglutination to $\frac{1}{128}$ whereas controls showed agglutination to $\frac{1}{4}$. Injection of killed suspension into controls gave no reaction but provoked a violent reaction in the patient.

Histological section of the lesion showed nonspecific granulation tissue with numerous gram-negative rod-shaped organisms. No evidence of syphilis or tuberculosis was found, although for a considerable time the lesion was believed to be a specific granuloma.

There seems no doubt at all that Longhi's case was a primary infection by *Ps. aeruginosa* and the appearance of the organism in the urine indicates a transient bacteremia just as, in our case, the presence of the organism in the abscess, peritoneal discharge, and stools, is presumptive evidence of bacteremia.

According to Kerby,[2] bacteremia in children is a rare disorder and he was only able to accept 39 cases in the literature. Geppert and others[1] claimed that infections had become more frequent and of graver character as a result of the widespread and indiscriminate use of antibiotics and describe 8 cases of destructive lesions of the skin, bowel, and respiratory tract in which 3 patients died. In our case there was no record of the mother having received antibiotics.

The source of the infection in our case was not known. It may have originated in the umbilical cord or have been acquired by ingestion. According to Ocklitz and Schmidt,[4] the organism may even be present in the intestine of the fetus before birth. The stage of the granulation tissue was consistent with infection having occurred at about the time of birth.

SUMMARY

A case of suppurative orchitis due to *Ps. aeruginosa* in a child of 10 days of age is described in which there was presumptive evidence of bacteremia. Operative excision was followed by recovery.

We are indebted to Mr. Adrian Wilson for the photograph.

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BRITISH-AMERICAN PEDIATRICS AND CHILD CARE; GENERAL PRACTITIONERS, CONSULTING AND PRACTICING PEDIATRICIANS; PEDIATRIC EDUCATION

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UNTIL 1911, when the Lloyd George medical panel law was enacted in England, British and American pediatric practice and child care were quite similar.[1] There were very few pediatricians in either country, and they were solo consultants connected with charity hospitals, who also saw private pediatric patients referred to them by general practitioners for diagnosis and advice. The treatment usually was carried out by the general practitioners, and only rarely by the pediatricians. None of the British or American pediatricians of this pre-1911 era accepted children for continuous routine care and supervision which was provided, if at all, by the general practitioners and Health, Welfare and District Nurses and Visitors, Child Health Officers, Health and Welfare Centers,[2] School Clinics,[3] nurses qualified as midwives (SCM), and later by the home care, premature nurses, such as those trained by Dr. V. Mary Crosse[4] in Birmingham. As a matter of fact, mothers, general practitioners, and consulting pediatricians did not consider routine child care necessary. Some still are of that opinion.

The private consultation work of this period developed because general practitioners referred children to pediatricians for the chief and often the only reason that they were children and growing, developing human beings with their own specific problems[5, 6] which were difficult to understand, and not micro-adults[5] or miniature men or women, just as every physician now refers dogs to veterinarians because they are different animals. Later, consultations changed to a "disease" basis—thus a general practitioner would refer children to a pediatrician with a special knowledge of diabetes, epilepsy, cardiac disease, etc.,[7] a custom which many of us deplore, because pediatrics is the last stronghold of the general point of view in medicine.[8] Other specialties, and even general practice, have their splinter subspecialties.

EVOLUTION OF AMERICAN PEDIATRICS

About 1911, some American consulting pediatricians began to provide routine care for children, like that of general practitioners, as a *secondary* activity, in addition to their consultation practice, e.g., Fife and Sinclair in Philadelphia, and Saunders, Zahorsky, and Tuttle in St. Louis, among others.[7] This trend was gradually rising before World War I, but spread more widely after it. Perhaps part of the impetus was the experience with French puericulture gained by the

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younger consulting pediatricians sent to France during World War I by the American Red Cross to help with the care of the French War Orphans. Several other factors are also responsible for this change in American pediatrics from solo consultations to child-care practice. For example, some consulting pediatricians recognized the need, demand, and market for systematic, periodic supervised child care and made this field their *primary* occupation, rather than a side line. J. H. Mason Knox was one of the leaders in changing pediatrics from the diagnosis of the diseases and the care of sick children to what we know now as *child care.* He let it be known, early in his years of practice, that he would be glad to see well children for general health supervision. The idea of inviting visits from healthy children and charging for them was then so unorthodox as to be considered unethical, and the legend persists that there was outspoken professional sentiment against it.[9] Lucas in San Francisco, Royster in Norfolk, and others commenced seeing children from birth to the age of 2 or 3 years at frequent intervals, with advice to the mothers about feeding habits, growth, development, inoculations, and so forth, sometimes for a monthly or annual fee.

"Well-baby" conferences were started before World War I and the "summer round-up" for children entering school was soon extended throughout the entire period of childhood.[9a] The pediatricians early recognized that the environment is a potent influence on the life and welfare of the individual and they sought those elements in the environment which could be modified favorably, e.g., milk supply, school desks and lighting, poison sources, causes of accidents, etc., in order to avoid placing the individual at a disadvantage so far as health was concerned.[9b]

This trend has been so marked that the erroneous view sometimes is expressed that the practicing pediatrician is the only person who can give the child the professional care and advice he needs in sickness and in health as he travels the confusing path of growth and unfolding personality, on the ground that only a pediatrician knows children from birth throughout adolescence, and his concept of his responsibilities has broadened to include emotional and social reactions. Moreover, because of the intimate relationship of the practicing pediatrician with the parents, he has become in many instances quite logically the family health counselor. As a result, the United States may soon have a new type of family doctor, who does everything except obstetrics. Such doctors usually do not treat the adults in the family but know sufficient medicine to refer them to general practitioners or specialists. Because of their pediatric training in preventive medicine, they also are among the most active leaders in community health and school responsibilities.[6] *Many who are expert* in ministering to adults are rarely by interest, training, or temperament adept in handling the problems of childhood.[6] Some American mothers say that the difference between visits by a general practitioner and a pediatrician is that the former examines only the complaint area and is solely interested in ill patients while a pediatrician studies the whole child and wants to keep him healthy. Another

American argument in favor of child care by a practicing pediatrician is that by having a smaller field he probably has a wider knowledge of children than the family physician who must keep up with the care of patients from birth to old age. If a child has a complicated illness, however, the practicing pediatrician refers the patient to a hospital, because diagnostic facilities are available there. In Britain the same sequence holds, except that it is not a specialist who sees the child in the first instance, but the family doctor.

This movement snowballed before the pediatric academicians recognized it and shifted the type of training to meet the demand. For example, in 1926 Lucas wrote to one of us, living in the Hopkins ivory tower, for a pediatric resident to share his growing load of routine child care. The resident who accepted this appointment, like all residents of his generation, had been trained to diagnose and treat the ills of children, and was frustrated by seeing the same well children every month or two. Some pediatric departments still ignore the need for training in routine child care. The demand for this service continued, however, and the number of pediatricians mushroomed.

Very soon, the American mothers realized the benefit of this complete, continuing, comprehensive, and total child care, health supervision, and psychological, social, and vocational rehabilitation.[9c] They are so convinced of the value of well-baby care that attempts to discontinue such appointments during the wartime shortage of doctors led immediately to such pressure that they had to be resumed. Many mothers displayed ingenuity or adopted the subterfuge of having a "sick baby" to obtain appointments. Once in the doctor's office, they managed to obtain a "well-baby checkup." Although well-baby care is now part of the American way of life, well-child care is being neglected. Only 14 per cent of the patients in the average pediatrician's practice are over 6 years of age.[9d]

Another factor in this trend from general practice is the American Specialty Boards, which were originally established to protect the public against self-acclaimed and often untrained specialists, but which have now acquired such prestige and have become so attractive, especially to recent graduates, that they have done more harm than good by depleting the supply of general practitioners, and by making the specialists and the public believe that specialists are exalted beings, a cult largely started by the surgeons though the other specialties are becoming increasingly guilty. As a result, many mothers believe that only a specialist is reliable and they lose confidence in their family doctor because he is not a specialist, and transfer to a practicing pediatrician, mainly because he is a specialist.[10]

The American general practitioners, on the other hand, either did not recognize this development or were not interested in it. They actually hastened the transition of routine child care from the family doctor to the practicing pediatrician, because some of them, British as well as American, are not fond of babies, and in fact are sometimes afraid of them. Lack of experience in a subject causes dislike of that subject. Some family doctors feel insecure in giving routine child care because they have been too busy to follow the pediatric literature. In those cases, the general practitioners or obstetricians suggest to the expectant mother that she engage a practicing pediatrician. Even without being referred by physicians, many women make such arrangements on the advice of other mothers, particularly those who have read the lay medical journals, e.g., *Time* and the *Reader's Digest*. This movement also was given impetus by the White House Conferences on Child Health, especially by President Hoover's 1931 Children's Charter* and by the Emergency Maternal and Infancy Care (EMIC) program established by the U.S Children's Bureau in 1943 during World War II. Before EMIC, many parents did now know that a pediatrician was not a foot doctor.[6]

Another factor in increasing the number of pediatricians at the expense of the general practitioners, which has not been sufficiently emphasized, is that after the Second World and Korean Wars, the United States gave every military physician sufficient money to return to hospitals and medical schools for retraining. Practically all of them used this "GI money" to become specialists. For example, 40 per cent of the Duke graduates before the war entered general practice and within five years after the war only 7.7 per cent.

As a result of some or all of these factors, American pediatrics, at present, consists of a few consulting pediatricians attached to hospitals and university clinics as members of a consulting team, usually on full-time salaries as in Britain, and a rapidly growing number of practicing pediatricians who, with rare exceptions, specialize in the care of children up to a certain age, and whose major activity is the maintenance of child health and the prevention of diseases.[11] Almost every community of 15,000 or over in the United States now has a pediatrician. In North Carolina, the number of pediatricians has grown from 11 to 131 in twenty-five years; some towns in which a pediatrician could not make a living a few years ago now have four child-health practitioners who are so busy that they have asked Duke University Medical Center for one or two more. The number of these new practicing pediatricians in the United States has grown to the present 5,981, who have been certified by the American Board of Pediatrics.[12] Of the 218,061 American medical school graduates, 6,567 limit themselves to pediatrics and 2,156 practice part-time pediatrics—a total of 8,723.[13] To bring this large group together, the American Academy of pediatrics was organized in 1930, and now has around 4,500 members in the United States.[13] In 1946-1947, 11 per cent of American children received medical care exclusively from pediatricians.[6] In 1948, the health care of 50 per cent of American children was fully or partially supervised by pediatricians in private offices, clinics, or through social agencies. Now the percentage is approximately 65.[13]

Actually, but unfortunately, in addition to the original British-American consulting pediatrician attached to a teaching clinic or hospital, and the practicing pediatrician who is a child-care specialist and family counselor, a third variety of pediatrician has arisen with a huge office, innumerable cubicles, dozens of nurses and secretaries. He provides excellent child care but on a completely impersonal, commercial, and "production line" basis. Many of them purposely build their examining cubicles so small that the mothers cannot get in and delay the procedures by asking questions. They later give these mothers an opportunity for brief questions, with or without a fee, by setting aside certain hours during the day for telephone calls. This is carrying efficiency too far, and taking all of the humanity out of pediatrics. Perhaps the mothers eventually will resent this treatment and return to general practitioners for the health care of their children.

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*President Hoover's White House Conference on Child Health ond Protection, "recognizing the rights of the child as the first rights [illegible] to prenatal, [illegible] th protection [illegible] ce, and periodi [illegible] y child, regardl [illegible] wherever he [illegible] of the Americ [illegible]

CHILD CARE BY GENERAL PRACTITIONERS

It is physically, numerically, and financially impossible for the supply of practicing pediatricians, large though it seems in this country, to provide child care for all of the present forty-seven million children scattered throughout the United States—over 5,000 children per pediatrician. With four million American babies being born each year,[14] the child health problem is growing faster than the rapid increase of pediatricians. Furthermore, in spite of the rise of pediatrics, many American parents still desire a family doctor, or family health coordinator. Unfortunately, from the end of World War II to the present, the number of general practitioners has been depleted by death with very few young replacements. Fortunately, however, among the most recent American graduates, the percentage going into general practice is increasing, possibly because the specialties are becoming crowded. It is hoped that these youngsters will practice pediatrics and geriatrics. There is no reason, in spite of previous quotations to the contrary, why a family doctor cannot supply routine care of children, as well as of adults. There are still 60,000 American general practitioners with a genuine interest in children,[15] a quality which is essential to good child care. Some of these family doctors had been graduated prior to 1930, when there was limited pediatric training in medical schools or in internships, but they have kept up with the growing mass of pediatric material, and have attended postgraduate courses in the new and preventive aspects of child care, such as that at the Southern Pediatric Seminar at Saluda, N. C., and those organized by the American Academies of General Practice and Pediatrics, and the Harvard, Washington, Duke, and other medical schools.

The general practitioners who have been trained since 1930 have had better, but still inadequate, medical school and hospital instruction in pediatrics, but many of them have continued their pediatric interest through refresher courses. There is no need for pediatricians in the localities in which these family doctors practice because they do everything a pediatrician can do. In many instances they do a better job of child care because they treat all members of the family. These localities are slowly increasing, thanks to better pediatric instruction in medical schools, more time allotted to the children's outpatient departments and well-baby clinics in rotating internships, and, last but not least, the excellent postgraduate programs. Instead of the usual query: "Is the general practitioner doomed?"[11, 16] some believe that the pediatricians in the United States are destined to be crowded out by the general practitioners who like children and who have kept up to date.[17]

STATUS OF BRITISH PEDIATRICS

Most members of the British medical profession still believe that child care should be only in the hands of the general practitioners and that pediatricians should only be consultants attached to hospitals. The prevailing British view of child care has been summarized by the late Sir James Spence[3]: "First and foremost it would become fully accepted that the intelligent care of children requires one doctor for the whole family—requires in fact a family doctor. This leads us naturally to reject the view, which is growing in the U.S., that the home care of children should be in the hands of separate paediatric practitioners. We feel that such a development would not be in the best interests of family life and domiciliary practice in Britain."

When the National Health Act was passed, British private pediatric consultation practice almost disappeared, and the British pediatricians usually see only the patients referred to the hospitals to which they are attached. Some British pediatricians, however, still have private practice in addition to their salaried National Health appointments, and they are consulted by the family doctor and the parents in case of difficulty.[18] The British pediatrician's private practice is a part-time occupation, is mostly consultant, and involves much less day-to-day doctoring of individual children, much less telephoning, little night work, and little care of healthy children.[18] In most British towns it is difficult for a pediatrician to make a living solely from private pediatrics,[18] in contrast to the American practicing pediatrician, who makes a reasonably comfortable income.

Everyone in Britain is entitled to free care under the National Health Service, but there are still some mothers who do not like sitting in hospital waiting rooms, and can afford not to; others who want to be sure they will see the pediatrician and not one of his junior assistants; and some who desire a more leisurely consultation than they get in a clinic with the doctors working under pressure.* There are also parents whose children suffer from recurrent upper respiratory tract infections, enuresis, and other long-standing problems, and who want special attention. The very worried parents of children who steal or show some other severe and perhaps embarrassing behavior disorder often seek private advice.[18] In addition, there are in Great Britain some mothers, mostly from the United States, who want a pediatrician to follow their babies from birth through adolescence because they cannot distinguish between a British general practitioner who is interested in routine child care and those who have little or no desire to supervise healthy children. If these mothers inquire of the British consulting pediatrician who is always attached to a hospital, however, they are usually referred to a general practitioner who is known to be interested in children, and, once they understand the arrangement, these American mothers seem to like it very much. This doctor also will look after the whole family and will certainly consult the hospital pediatrician if he is worried. There is, of course, the other side of the problem: British mothers in the United States. For example, a very intelligent English woman who married and went to Chicago found it difficult to get the help she needed. When the whole family was ill she had trouble in finding a family doctor to visit her sick child as well as the other members of the family.[20]

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*Private Health Insurance, similar to American Blue Cross and Blue Shield plans, to provide medical and nursing expenses for those who prefer private care to the National Health Service, is expanding in Britain at an annual rate of 30,000 new subscribers[19]

Another important difference between British and American medicine, and no one knows which is preferable, is the strictly limited British opportunity for specialization; a pediatrician, no matter how well trained, cannot, or at any rate does not, set himself up as a pediatric consultant until there is a hospital vacancy. His only alternative under the National Health Service is to become an assistant to some established general practitioner on a one- or two-year contract without any assurance of being made a partner. Perhaps if additional financial efficiency awards were given to trained pediatricians who are in general practice, the discontent of these men would be reduced and the general care of well and sick children in Britain would be improved. These doctors could devote their time chiefly to the care of children but also be available for diseases in the older age groups so that they would in effect be family doctors with a special knowledge of children. The "unemployed registrar" problem may in this way be a source of strength in the future if it is handled sympathetically from the financial point of view. Apart from combining the advantages of the family doctor with a better knowledge of child-health care, the educational value of such people spread throughout the community cannot be ignored.[21] It also would be interesting for some enterprising British pediatrician to try the American type of private child-care practice without any subsidy of salary from the government.

The status of a British general practitioner also is "frozen,"[22] a situation which has grown worse since the British nationalized their health services in 1948. A family doctor who acquires training as a specialist must wait for someone to die and vacate one of the limited number of hospital appointments so that he and many others can apply.

DISCUSSION

Both in Britain and in the United States, the responsibility for child care should be in the hands of one individual, the family doctor in Britain and the general practitioner *or* practicing pediatrician in this country. The chief argument for child care by the practicing pediatrician is that he can provide complete care himself, while the general practitioner is hampered, as Spence[3] recognized, because "a great number of authorities, institutions, agencies, societies and professions share in arranging the health and welfare of children. There are so many of these agencies that they often are at a loss to know how to bring their aids and encouragements at the right time to the families which need them." Under the British program, "the child-welfare center remains the chief agency for advising mothers about the care and feeding of their children in health.[3]' Some of the mothers also go to the center for advice on minor illnesses in their children. An analysis of attendances at welfare centers showed, however, that "one third of the infants did not attend; one third attended occasionally; and only one third attended regularly for all or some part of the year."[3]

Most Americans believe that a compromise between the British and American systems is preferable to either extreme, i.e., child care should be in the hands of general practitioners if, and only if, they have an interest in and knowledge of child care, but that if no such family doctor is available, child care should be in the hands of practicing pediatricians trained to provide this skill, and that under this "complementary" program, the health of children is better and the morbidity and mortality rates are lower.

PEDIATRIC EDUCATION

The most important factor in British, American, or any other system of child care is the adequate training of general practitioners, and appreciation by students of the value to the community of well-trained and interested family doctors. In spite of the trend in America toward greater numbers of practicing pediatricians, much child care, in the United States as well as in Britain, as previously mentioned, must still be provided by family doctors; therefore the medical schools must increase their efforts to provide them with a sound training in this field. In order that medical school faculties and hospital staffs may furnish adequate undergraduate and postgraduate training so that general practitioners and practicing pediatricians can supply the best type of child care, they should be alert to the best interests of children and to the desires of the mothers. The task is easier if these interests and desires coincide, as they usually do. For example, mothers have always wanted to room with their hospitalized children, and we are just now learning that rooming-in is beneficial for ill children[3] as well as for the newborn,[23] and that our former strict visiting rules and nurseries for the newborn[24] are harmful.

Most teachers of pediatrics are agreed that all medical students should have some experience, preferably early in their course, with children and families in a normal environment, namely, their homes. This experience was lost when "outside obstetrics" was abandoned.[25] Some medical schools are assigning students to families as advisors, and others, with the help of the British College of General Practitioners[26] and the American Academy of General Practice, are stimulating interest in family practice and child-family relationships by preceptorships with outstanding general practitioners.[6, 27] A few schools are experimenting with courses in General Practice.[28] The chief aim of an undergraduate pediatric teaching program should be to "sell" child care, i.e., to simplify the subject so that students will like infants and children instead of being confused by being crammed with data about growth, development, numerous infant feeding mixtures, and rare diseases. They should be taught to recognize the more common illnesses in the outpatient department rather than listen to learned discussions on the usual collection of rarities in the pediatric wards, which are of such great interest to the professors. The pediatric curriculum must also provide training in preventive pediatrics and routine child care.

In Britain, although several university pediatric chairs carry the title of Professor of Child Health, and some of the consulting pediatricians have diplomas in Child Health (D.C.H.), the emphasis in pediatric graduate training (residencies and registrarships) is entirely on pediatrics as a consultative specialty. In the United States, although the first pediatric department for the prevention of disease was established in 1914 in Philadelphia by the late Howard Childs Carpenter, who devoted most of his life and efforts to the development of child-health care,[29] much of the pediatric graduate training (residencies) also is in diagnosis and treatment. Some American practicing pediatricians are still frustrated, discontented, and intellectually bored,[6, 30] because as residents they saw *only* the *interesting* clinical material and rare cases in the wards of a large hospital and are now dissatisfied by not seeing similar patients in their practice. To remedy this situation, which was first recognized in 1926, as previously mentioned, the Duke pediatric residency, which was started in 1930, emphasized outpatient, well-baby, and school-clinic experience. Few American pediatric exresidents are dissatisfied with the type of practice they are having, which is 75 per cent preventive pediatrics, if their residencies have stressed outpatient teaching,[31] well-baby, school, and special clinics, affiliation with neighboring special and general hospitals, training schools for retarded children,[6] and, last but not least, home care preceptorships and pediatric office apprenticeships,[26, 27] even if only for a week or two. House visits enable the general or pediatric practitioner to perform better his increasingly exacting duty of child guidance. In the home he can tell whether the mother is a neat and orderly perfectionist (perish the thought!); or whether *she is so sloppy as to pile an electric* hotplate on a 'phone book by the baby's bed to boil some water when he has croup (perish the baby!) or whether daddy reads the paper or watches television while the doctor examines his sick child; or, per contra, whether daddy is the bossy, interfering type. This a pediatric consultant cannot do.[32] Too often pediatric hospital training has equipped the residents only for the care of seriously sick infants and children—"that vitally important 10 per cent"—and for certain types of research, but not for the care of the run-of-the-mill well babies, nor of those with sniffly noses, bronchitis, "strep" throat, otitis, diarrhea, measles, eczema, "colic," etc., who should never see the inside of a hospital, and who comprise the great majority of private patients.[32]

The training of two types of American pediatricians has also been suggested: (1) a practicing pediatrician whose interest and emphasis in life are centered on the routine care of children, and who is trained primarily in the physical, emotional, and psychological aspects of preventive pediatrics so that he can recognize and treat minor physical and mental illnesses which constitute the bulk of pediatric practice, and (2) subspecialists or superspecialists, with their focus on an organ, e.g., the heart, or on special conditions, such as allergy, dermatology, hematology, pediatrics of the neonatal period, neurology, etc., and who are primarily interested in the more rare or unusual conditions.[33]

Perhaps the most neglected field of pediatric education is that of refresher courses for general practitioners. As Spence[3] has shown, the difficulties and uncertainties about the nature and type of acute illness in infancy demand from the family doctor a high level of diagnostic skill and therapeutic experience for which he requires special undergraduate and postgraduate training and without which the quality of medical care will be inadequate. The advance of knowledge about disease in childhood has been so rapid in recent years, and is continuing at such a rate, that regular postgraduate teaching of family doctors has become a great responsibility of the universities.[3] Unfortunately, some of the medical school pediatric faculties do not know the type of postgraduate training which a general practitioner needs or desires. Equally important is the failure of some family doctors to realize that they need refresher courses. However, the British College of General Practitioners[26] and the American Academy of General Practice are cooperating with the medical schools and teaching hospitals so that the content of the postgraduate training is more nearly meeting the situation.

Both British and American medical educators must also solve the following problems: (1) how to teach undergraduate medical students and postgraduate physicians so that they can provide better child care as general practitioners or pediatricians; (2) how to maintain the present progress[34]; (3) how to lower the mortality and morbidity rates even further, especially for accidents[35] and poisoning[36] (the highest causes of childhood deaths), cancer and leukemia[37] (the second commonest causes), and conditions among infants in the first month of life (the perinatal mortality is 43 for 1,000 live births,[38] and even in the better hospitals has not been reduced for the past seven years[39]), and (4) how to educate children so that child delinquency and later neuropsychiatric breakdowns can be avoided.

CONCLUSIONS

Family doctors and practicing pediatricians must "coexist" and work together for the benefit of child health. Both groups are necessary and equally important. British and American medical schools and hospitals must train both groups so that the job gets done by providing better and less boring courses in child care, and demonstrating their value to undergraduate medical students and interns, and also by organizing more and better refresher courses for general practitioners who desire to keep up with the advances in this field. Radical measures are needed to afford more experience for interns who plan to go into general practice.[6] Pediatric residencies must shift their emphasis from the rare and difficult diagnostic inpatient problems to the run-of-the-mine outpatients.

Obviously teamwork is essential for this comprehensive and continuing care. Physicians, nurses, psychologists, psychiatrists, dietitians, occupational and physical therapists, students of medicine and nursing, schoolteachers, scout leaders, and, last but not least, social workers all must unite and accept the total and continuing responsibility for the health of the individual or the family as a unit in order to safeguard children from conception through adolescence. All of these workers must be interested in the child as an individual with personal, family, and environmental problems.

Equally obviously, any team, athletic or medical, needs a captain, and he or she should not be selected because of having an M.D., Ph.D. in Psychology, or M.S. in Nursing, but rather on the basis of having an instinctive love and understanding of children, and an ability, like that of Osler, to make each patient feel that everyone on the team is primarily interested in his or her welfare.[40]

The most important factors are (1) the education of nurses, physicians, and the public in the need for this total care and in the value of teamwork,[40] and (2) a definite plan of continuing and progressive supervision in which the patient, the family, and the team participate.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS was the first Children's Medical Center admission of this 6-day-old white male infant, with the chief complaint, since birth, of cyanosis on crying. The patient was the result of the first pregnancy of a healthy 24-year-old woman. The pregnancy and delivery were completely normal. The child breathed and cried spontaneously, but duskiness was noted immediately. The birth weight was 8 pounds 2 ounces. While in the newborn nursery the child continued to appear dusky, and the lips, hands, and feet were cyanotic when he cried. The baby did well in the nursery and the cyanosis decreased in intensity. An electrocardiogram was done; this was abnormal and the child was sent to The Children's Medical Center for further evaluation.

The family history was noncontributory.

On admission the temperature was 99.6° C., the blood pressure by the flush method 52 mm. Hg in the right arm, 54 mm., in the left arm, 62 mm. in the right leg, and 66 mm. in the left leg. The pulse rate was 160 and the respirations 54 per minute. The infant was well developed, well nourished, and in no distress, but cyanotic when not given oxygen. The chest was clear to percussion and auscultation. The examination of the heart showed a right ventricular type of impulse. The first sound was not remarkable; the second sound was heard best at the left sternal border where there was also a grade I systolic murmur. The liver was palpable 4.0 cm. below the right costal margin. It was not pulsatile. The spleen tip was palpable. There was early clubbing of the fingers and toes. The remainder of the physical examination was noncontributory.

On laboratory examination the urine was normal. The hemoglobin was 18 Gm. per cent, the peripheral leukocyte count was 23,650 per cubic millimeter, with a differential smear of 48 per cent polymorphonuclear cells, 8 per cent basophils, 28 per cent lymphocytes, 12 per cent monocytes, and 4 per cent eosinophils. The platelets were normal in number. The serum nonprotein nitrogen was 39 mg. per cent. The Hinton reaction was negative. Fluoroscopy of the heart revealed a globular shadow, at the upper limit of normal in size, with an elevation at the apex. There was a marked depression in the region of the pulmonary artery and no main pulmonary artery could be identified. The intrapulmonary vasculature was decreased in prominence. The right atrium was increased in size. The aorta was prominent and normal in position. An electrocardiogram showed right ventricular hypertrophy, abnormal for the age. The ST segment and T waves were also abnormal.

The infant, while in the hospital, was gradually weaned from oxygen therapy. He was given digoxin and Gantrisin. He did well and was discharged from the hospital after a nine-day stay.

He was seen frequently in the Cardiac Clinic and continued to do well. The systolic murmur increased in intensity and a continuous murmur was heard by some observers. The cyanosis continued and the size of the liver remained unchanged. The electrocardiograph displayed changes of a progressive increase in the right ventricular pattern and a P pulmonale. Right bundle branch block and digitalis effects were present in all tracings. The cardiac fluoroscopy findings remained unchanged. At 10 months of age, nineteen days before death, the infant was seen in the clinic. He weighed 16 pounds and, though no murmurs were heard, the general condition was unchanged.

Eight days prior to death, the child had two mild and one severe cyanotic spells, which responded to morphine. On the day of death, another cyanotic spell occurred while attending the clinic. Then no murmur was heard and the liver was 5.5 cm. below the costal margin. Morphine and oxygen were given, without benefit, and the infant died, on admission to the hospital, at 11 months of age.

DISCUSSION

DR. PATRICK A. ONGLEY.*—May I first make a few random interpretations of the data as given?

There was said to be a right ventricular type impulse. What is meant by that is that somebody felt the maximal impulse at the xiphoid. That does not mean that this is entirely right ventricular. If there are two ventricles and one feels the maximum impulse at the xiphoid, it is probably right ventricular, but if there is only one ventricle—as in a tricuspid atresia, or single ventricle from any other cause—then you may feel the maximum impulse at the apex or at the xiphoid, so I think it would be correct if one said that this was a xiphoid-impulse. The first heart sound was described as being not remarkable, and the second sound was loud at the lower left sternal border. We are more interested in knowing what the second sound was like at the pulmonary area, and if it was a split sound or a single second sound.

DR. PETER AULD.—The pulmonary second sound was single.

DR. ONGLEY.—Was it diminished at the pulmonary area? If the second sound is split, that usually implies that there are at least two functioning valves. If there is a single second sound, one valve may be functioning well (which you can hear) and there may be one which you cannot hear. The murmur described was a grade I soft systolic murmur over the lower left sternal border. That does not help us at all because any normal person can have a grade I systolic murmur at the lower left sternal border. A suggestion of early clubbing of the fingers and toes was reported. We usually do not see true clubbing until at least a few months after birth, usually five or six, so I think the suggestion of early clubbing in a patient who is only mildly cyanotic does not help us at all. I would like to know the degree of cyanosis. It seems that it was not particularly marked at any time. Would that be a fair statement, Dr. Auld?

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*Dr. Patrick A. Ongley was formerly Instructor in Pediatrics, Harvard Medical School, and Assistant Cardiologist, The Children's Medical Center.

Dr. Auld.—That is correct.

Dr. Ongley.—I have just now looked at the electrocardiogram. The term P pulmonale usually refers to rather tall P waves, more than 2.5 mm. in height in Leads II, III, and those from the right chest. It is usually thought to mean right auricular hypertrophy. However, the P waves are not particularly tall in Leads I and II and, in fact, are just as big in Leads V_2, V_3, V_4, and V_5. I think that all we can infer from this is that we have atrial hypertrophy, but we do not know whether it is right or left, after looking at the tracing. The electrocardiogram, while it shows right ventricular hypertrophy, does not show the nice tall, narrow, right ventricular potentials which you see in pure pulmonic stenosis. It shows a rather wide QRS complex, which is the type that we sometimes see in a single ventricle.

Now let us consider the x-rays. There are certain things that I would like to ask Dr. Wittenborg. First: Are you sure this is the right atrium? Second: In your reports you say that the position of the aorta is normal, and I would like to know if, in the lateral film, it could be anterior to the normal position? In other words, could it be transposed? Third: Did you see a right and left pulmonary artery, or do you think there is a collateral pulmonary arterial pattern?

Dr. Martin H. Wittenborg.—The best films, Dr. Ongley, were taken at 6 days of life. We have a definite globular configuration in a heart which is only slightly enlarged in transverse diameter. The waist normally occupied by pulmonary artery is exceedingly narrow. This would imply that the pulmonary artery is markedly hypoplastic, completely absent, or that it is malposed. On the oblique films there was no unusual widening noted at the waist, so that it is assumed that the pulmonary artery is hypoplastic or absent. The aortic arch is on the left and the aorta descends in the normal manner. At this age it is impossible to determine accurately, by fluoroscopy, slight anterior take-off or slight dextropositions of the aorta. The pulmonary vasculature is definitely diminished, the vessels being small in caliber.

Later films show very little increase in the size of this heart, the shape remains the same, the vasculature remains diminished, and the right auricle is not demonstrated. The fluoroscope indication is that the heart was unduly prominent on the posterior lateral aspect, toward the posterior axillary line; when you rotate the patient, the right auricle would lie posteriorly.

Dr. Craig.—Did you see the left atrium?

Dr. Wittenborg.—No mention of enlargement of the left atrium is made, but the heart must have been unusually prominent posteriorly on the right. For this reason we mentioned a selective right auricular enlargement. We tend, in this hospital, to pay little attention to auricular enlargement because we find that it is of little value in the differential diagnosis. Especially, we do not try to distinguish the right from the left atrium. I think the films should probably be interpreted as showing prominence in the region occupied by atria.

Dr. Ongley.—At the time this child entered the hospital, the first diagnosis one would consider would be a tetralogy of Fallot, that being a common cause of cyanosis with evidence of right ventricular hypertrophy, a protruding apex, and a diminished pulmonary vasculature. What is against this diagnosis? There are two things, primarily. The first is that he does not have a murmur which really sounds like a pulmonary stenotic murmur. There is only a soft grade I murmur along the lower left sternal border, yet that does not entirely rule out a tetralogy. If such children are examined during a cyanotic spell, or when breathing is particularly heavy, it is difficult to hear the murmur. Assuming that the persistently enlarged liver has been due to congestive failure, then we must assume that we have a tetralogy in failure. We have not seen congestive heart failure in tetralogy of Fallot in childhood, so I think we will discard that diagnosis.

The second lesion that one thinks about is valvular pulmonic stenosis with an intact ventricular septum, and a right-to-left shunt through a patent foramen ovale. The finding against this is that no pulmonary artery is seen. Now it is true that we have seen cases of pure pulmonic stenosis which did not show any obvious pulmonary artery by roentgen examination. One 6-month-old girl had a markedly enlarged heart, and as the heart enlarged it obscured the origin of the pulmonary artery—but we do not have that type of x-ray picture here.

The third diagnosis would be tricuspid atresia. In our series of tricuspid atresias we have two which showed right ventricular hypertrophy on the electrocardiogram. If you are going to diagnose tricuspid atresia in the presence of right ventricular hypertrophy, you will be wrong so often that is not going to make very much sense. I would prefer to disregard tricuspid atresia as a possible diagnosis, even though there is a very remote chance that this may be the proper diagnosis.

A fourth possibility is a true truncus arteriosus. There is not too much that is against a true truncus—one large single vessel is identified coming out of the heart—yet the patient was not very cyanotic in the early stages of life. When we see a true truncus patient who is not very cyanotic, we usually find very good pulmonary vasculature and a continuous precordial murmur. If the pulmonary arteries are very small, a continuous murmur may not be present. Even so, these patients are often considerably more blue than this child was. A truncus, I think, is a very distinct possibility.

Last, I really want to consider something else which is a little bizarre, perhaps. It puts me way out on a limb but would possibly explain everything that we find, including a cause of death. If we assume that there is no visible pulmonary artery segment on x-ray, then, as Dr. Wittenborg says, we either have no pulmonary artery at all, or we have a small hypoplastic one, or we have one which is completely displaced. Now, if we have a displaced one—in other words, a typical transposition—we then usually have pulmonary vascular engorgement, which we do not have here. If, on the other hand, we have a displaced pulmonary artery but with pulmonary stenosis, we should hear a pulmonary stenotic murmur—but we do not hear that either. We have to take things on their face value and are going to assume that we have pulmonary atresia. By pulmonary atresia we mean atresia of the pulmonary valve; we do not mean that the pulmonary arteries themselves, beyond that valve, are necessarily going to be absent. The developmental anomaly which causes the atresia of the valve is not necessarily going to cause disappearance of the entire pulmonary arterial system. If we have pulmonary atresia, then we are going to have to get some blood back to the lungs, somehow, and we have two choices, either through bronchial collateral arteries or through a patent ductus. Now, if bronchial collaterals are present, one may hear a continuous murmur out in the periphery of the lung fields, either in the axillae or over the back, but the only continuous murmur we have recorded here is one heard along the left sternal border, and we do not see any bronchial collateral pattern on the x-ray. Therefore, I am going to assume that we have a single ventricle, an aorta leading out from this, and then a ductus going down from this aorta to the pulmonary arteries. We now have the blood to the lungs, and we have to get it back to the left atrium. I am going to assume that the pulmonary venous drainage is normal, although in some cases of single ventricle with pulmonary atresia there is anomalous pulmonary venous drainage. Up to this stage I am reasonably confident of the diagnosis of a functionally single ventricle with one vessel—the aorta leaving this ventricle and the blood passing via a patent ductus arteriosus to the pulmonary arteries. From here, we must go on statistics.

If there is a single ventricle, then there is a great likelihood of a single ventricle with pulmonary atresia or, in some cases, aortic atresia. Here we think it is going to be pulmonary atresia because of the diminished vasculature. Isolated single ventricles with normal atrioventricular valves are rare. Mitral atresia or tricuspid stenosis is commonly present. Since there is no diastolic murmur suggesting tricuspid stenosis, we are going to assume that this patient has mitral atresia as well.

This brings us to a consideration of the atrial shadow in the x-ray. I would like this to be a large left atrium since, when mitral atresia is present more commonly, there is a patent foramen ovale rather than a secundum-type atrial septal defect. If the foramen ovale becomes stretched a little, a left-to-right shunt through this stretched orifice, rather than through a true secundum-type atrial defect, may be present.

These, then, will be our anatomical diagnoses—single ventricle, pulmonary atresia, a transposition of the great vessels, a patent ductus arteriosus, and a mitral atresia, probably with a patent foramen ovale.

Can we say now why the patient died? We have a reasonably good flow to the lungs. Anatomically we have a normal venous return, and we have a *functionally* trilocular heart—so the patient should not do too badly. Now, if this patient were a little older, I would think, first of all, of a cerebral abscess as the cause of death. There have been quite a few cases in the literature of this type of lesion with a cerebral abscess, but this child was only 10 months of age. On the other hand, if we try to assign death to a physiologic disturbance, a patent foramen ovale will give an increased pressure in the left atrium, and this is transmitted to give an increased capillary pressure and pulmonary arterial pressure. This could cause death in two ways. It could cut down the left-to-right shunt through the ductus and cause these anoxic attacks of blueness and death in that way—or a thrombosis could occur in the pulmonary artery, resulting in death.

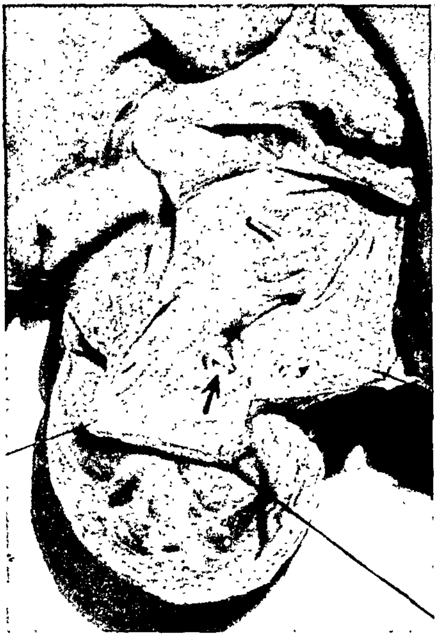

Fig. 1.

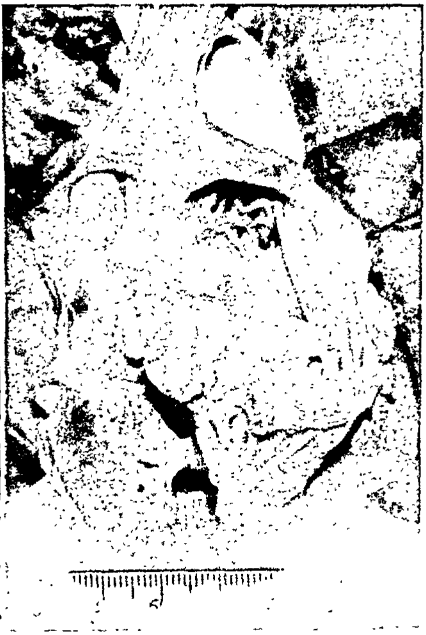

Fig. 2.

Fig. 1.—Heart. The left atrium is viewed from above. The endocardium is thickened. At the arrow is the mitral valve remnant leading to the hypoplastic isolated left ventricle.

Fig. 2.—Heart. The right atrium and ventricle are dilated, the ventricle is hypertrophied.

Dr. Craig.—Do you ever get pulmonary congestion with mitral atresia?

Dr. Ongley.—Well, I do not see why you couldn't get it secondary to difficulties with outflow from the left atrial chamber. Is there any venous congestion of the lungs?

Dr. Wittenborg.—I think that on the second film the vasculature is slightly more prominent, with pulmonary engorgement.

Dr. Louis K. Diamond.—Dr. Ongley, what therapy would you recommend for this child?

Dr. Ongley.—I am surprised that he lived this long. The average duration of life is about three or four months.

Dr. Craig.—This child, at autopsy, had functional mitral atresia with a very small mitral valve remnant opening into a minute isolated left ventricle, with no other openings (Figs. 1 and 2). The pulmonary veins were dilated, as was the left atrium; the endocardium of the latter was thickened. The aorta was transposed and the pulmonary outflow tract was atretic, both as Dr. Ongley predicted (Fig. 3). The pulmonary artery was of good size and the ductus arteriosus was patent, having a diameter of 3 mm. There was a pulmonary artery thrombus and resulting lung infarction. The latter may have been partially due to the increase in pulmonary venous pressure as a result of the absence of an adequate outflow from the left atrium.

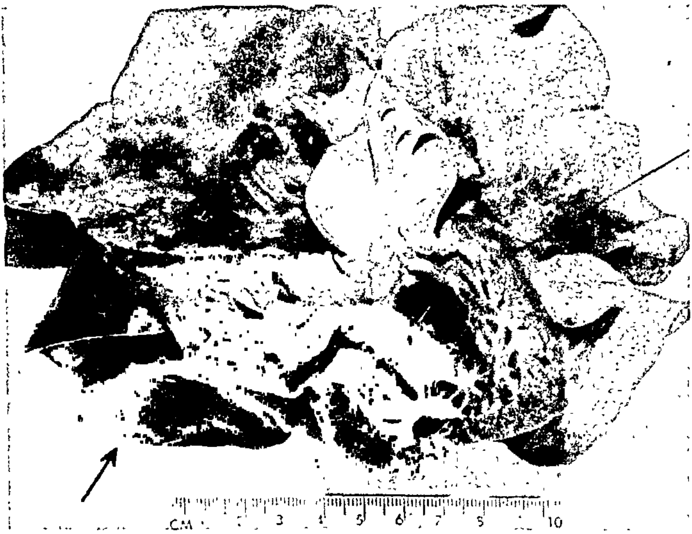

Fig. 3.—Heart and lung. The transposed aorta comes off the right ventricle anteriorly. The right lower lobe of the lung is infarcted.

The child had evidence of cardiac failure with passive congestion of the liver. Numerous stercoral ulcers were present in the bowel, which may be correlated with the child's history of constipation which was not brought out, I believe, in the clinical procotol. These ulcers may not have been of clinical importance.

The lesions of mitral atresia are, in many ways, complementary to those of absence of the tricuspid valve in that one may have transposition or hypoplasia of the outflow tracts of either ventricle. An incomplete summary of our autopsied cases of mitral atresia (in which there were eight examples) indicates that aortic hypoplasia was present in three, pulmonary hypoplasia or atresia in four, and, in one instance, the ventricular outflow tracts were of equal size. In five cases, the left ventricle was isolated, without connections to other heart chambers; in the remainder, the left ventricle was hypoplastic. Three had no atrial septal defect, though in one of these there was anomalous venous damage to the right atrium. In the reported cases with no free interatrial communication, the return of blood from the lung may pass through enlarged Thebesian channels, extra-atrial channels, or by the bronchial veins to the right ventricle. The duration of life in our cases of mitral atresia is, on the average, three to four months, as mentioned by Dr. Ongley. At autopsy we have seen one girl of 17 years, however, who had mitral atresia. In her case, a diagnosis of Fallot's tetralogy had been made. She succumbed with a pulmonary artery thrombosis after a Potts' aortic-pulmonary anastomosis.

In the case under discussion, the pulmonary artery was adequate in size for an anastomosis.

Dr. Abraham Rudolph.—In cases with a decreased pulmonary flow but with a large heart, there is almost always a complicated heart lesion. If an aortic-pulmonary shunt is performed to help these children, they usually succumb to the procedure fairly soon. With a shunt, a great deal of the blood which is going out through the aorta will come back to the ventricle, and the ventricle will have a tremendously increased amount of work to do. The ventricle often goes into failure within six months after operation. We have seen this with a single ventricle and a decreased pulmonary flow. If one had put a shunt into this baby, there would have been the extra problem of getting the blood back from the lungs to the right atrium.

One other interesting point is that in spite of the large pulmonary veins that were seen at autopsy, on the x-ray we could not really see any pulmonary veins, which again bears out the point that it is not the size in terms of anatomical size, but the size in terms of flow. This is of some importance because the flow through this must have been very small. I think Dr. Ongley did a wonderful piece of detection.

Dr. Craig.—After a shunt procedure in tetralogy of Fallot, is the work load of the right ventricle reduced?

Dr. Rudolph.—Well, actually this is something which people are thinking a great deal about in relation to the degree of overriding of the aorta. At one time it was thought that the degree of overriding was a significant feature. Then, suddenly, thinking changed and the relative resistance of the systemic circuit and the pulmonary obstructions were regarded as most significant as to the degree and direction of the interventricular shunt. However, when you consider the fact that if the aorta is overriding considerably, even if there is a fairly large ventricular defect, the actual streaming of blood must push blood from the right ventricle into the aorta. In the tetralogy patients, as a group, the ones who go into failure after shunt surgery (though perhaps Dr. Gross will not agree with me) are those who have marked overriding of the aorta and a large ventricular defect. On the other hand, with a very small ventricular septal defect, you may not actually do a great deal of good by a shunt procedure. If the aorta has little overriding, and the ventricular septal defect is small, putting in a shunt will not really help very much because the degree of shunt from right to left is quite small.

Dr. Robert E. Gross.—With some cases of the mitral atresias, with a large pulmonary artery, too much blood gets into the lung. These children will, eventually, if they live long enough, get right-sided heart failure.

Dr. Craig.—The usual embryological explanation for mitral atresia is the one which is given for tricuspid atresia —that there has been a deviation in the formation of the septum of the atria and ventricle, primarily of the ventricle, to one side, so that the atrioventricular canal is obliterated on the side of the atresia.

Medical Progress

HEMISPHERECTOMY IN CHILDREN

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INTRODUCTION

BOTH the pediatric practitioner and the neurosurgeon are frequently confronted by parents who raise very practical, important, and difficult questions. To the parent who must make a decision regarding such drastic surgery as a hemispherectomy, consequences are of primary importance. As unhappy as parents are with a child's hemiplegia, endless convulsions, and incorrigible behavior, the thought of surgery evokes certain anxieties and fears which must be dealt with by the pediatrician and/or neurosurgeon. The probability of surgical survival is always uppermost in the minds of parents whose children undergo such major surgery. The next question is usually, "What effect will such surgery have on my child's behavior?" The question of surgical survival can be answered objectively in terms of probability based upon statistical data. The question regarding consequences of surgery has until recently been answered within the subjective, personal, and anecdotal realm. A definitive study dealing with the consequences of hemispherectomy in children is yet to be done. A start has been made in that a number of studies have begun to utilize objective and standardized measures wherever possible. It is felt that while additional data need to be amassed and sufficient experimental controls utilized, there is sufficient data available at this time to enable the pediatrician to answer some of the questions posed by parents.

THE APPLICATION OF HEMISPHERECTOMY TO INFANTILE HEMIPLEGIA

Hemispherectomy is a relatively new procedure. The first cerebral hemispherectomy was done by Dandy, in 1923, at the Johns Hopkins Hospital, and this case first appeared in the literature in 1928[1]—just 30 years ago. Since that time, numerous case reports have appeared. Mensh and his associates[2] listed 32 publications between 1928 and 1951. These represented 41 hemispherectomies. While a preponderance of this surgery was applied to the adult suffering from infiltrating tumors of the subdominant hemisphere,[1-12] hemispherectomy has of late been utilized and applied to a specific group—the infantile hemiplegic.[13-26]

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Ford[27] classifies this condition as one of either acute infantile hemiplegia of obscure etiology or congenital hemiplegia. Regarding the acute type, Ford states:

> In the early stages of the illness the affected hemisphere may be so swollen that ventriculographic study may suggest brain tumor. Later, of course, atrophy becomes evident. Later the hemiplegia extremities become spastic and the usual deformities develop. The affected limbs do not develop as well as the normal limbs and years later may be very small and distorted. Tremor or athetosis may appear. In other cases, the focal signs may largely or completely disappear. Unfortunately, in almost half of all cases convulsive seizures recur from time to time.

The prognosis as presented by Ford is one of low mortality and is unfavorable in outlook for recovery. Epilepsy is said to follow in about half of all cases, and mental retardation is to be expected. This type of hemiplegia is said to result from a single gross vascular lesion of the brain.

The congenital form of hemiplegia is said to result from a birth injury. Intrauterine injury and disease are other explanations offered. Ford describes the clinical features of the congenital type as follows:

> Flaccidity of the paralyzed limbs is relatively more frequent in congenital hemiplegias than among those occurring later in life. In such cases, we find striking under development of the hand and less evident under development of the arm and leg. The hand is of childish appearance, but it is not in any way deformed. Due to the shortening of the leg the pelvis may be tilted and the spine may show a postural curve. The tendon reflexes are usually somewhat increased on the affected side, but this is never so striking as in spastic paralysis.
>
> In other cases, the paralytic limbs are very spastic since the muscle spasm develops when the bones are plastic, extreme deformity of the hand is produced.
>
> In almost all cases, there is mental deficiency—convulsive seizures occur in almost 40 or 50 per cent of all cases.
>
> Even severe hemiplegias of congenital origin may not be apparent until the child is several months of age.

The prognosis is said to depend upon the amount of injury to the nervous system. "Little improvement is to be expected. The presence of convulsions makes the outlook unfavorable, for deterioration often occurs in such cases."

It would certainly seem from the above that the prognosis of infantile hemiplegia accompanied by convulsive seizures is indeed gloomy. It is with this in mind that surgical intervention occurred. Krynauw[19] worked primarily with children and carried out twelve hemispherectomies over a five-year period. In all cases, hemiplegia per se was not a sufficient condition for surgery. Convulsive seizures and behavioral changes (uncontrolled emotional outbursts) were also evident. Thus, a triad of symptoms were considered before hemispherectomy was undertaken—hemiplegia, convulsive seizures, and the presence of lowered intellectual functioning and/or uncontrolled emotional outbursts as behavioral manifestations. Occasionally, surgery was undertaken in the absence of seizures or in the absence of emotional outbursts while the other symptoms were present. Thus, it was only a little over seven years ago that *any specific formulation* developed in the application of hemispherectomy to children.

FINDINGS

A survey of the American and British literature pertaining to hemispherectomies in children (ages from birth to 16 years) yielded 29 cases. Table I summarizes the data reported by each investigator. It is interesting to note that investigators differ in the amount and kind of information reported. For example, one investigator[19] relied on parental report and subjective evaluation of change in intellectual functioning. Another investigator[25] focused on the social adjustment of the child and reported no data regarding the particular hemisphere removed, the effect on the child's seizures, and hemiplegia. Still another investigator[23] concluded that intellectual functioning increases following hemispherectomy, yet gave no specific data to support his conclusions. While systematic and quantitative measures are at times lacking and like the blind men, each investigator touches a different part of the huge elephant, the impressions and findings that are reported do seem to indicate specific trends. Tables II-VIII present these trends.

TABLE I. EFFECTS OF CEREBRAL HEMISPHERECTOMIES IN CHILDREN

AUTHOR	AGE AT HEMISPHERECTOMY	SEX	HEMISPHERE REMOVED	CONVULSIVE SEIZURES	HEMIPLEGIA	INTELLECTUAL FUNCTIONING	EMOTIONAL OUTBURSTS
Krynauw (1950)	9	F	L	Gone	Improved	Improved	Gone
	?	F	L	Gone	No change	Improved	Improved
	3	F	L	Gone	Improved	Improved	Improved
	10	M	L	Gone	Improved	Improved	Improved
	2	M	R		Died		
	9	M	L	None before surgery	No change	Not reported	Gone
	2	F	L	Not reported	Improved	Improved	Improved
	15	F	L	Gone	No change	Improved	None before surgery
	14	M	R		Not reported		
	13	F	L		Not reported		
	7 mo.	F	L	Not reported	Improved	Not reported	Not reported
Cairns (1951)	7	F	?	Improved	Improved	Improved	Improved
McKissock (1953)	4	M	R	Gone	No change	Not reported	Gone
	11	M	L	Improved	Worse	Not reported	Gone
	4	M	R	Gone	Improved	Not reported	Gone
	4	M	L	Gone	No change	Not reported	Gone
	1½	M	R	Gone	No change	Not reported	Gone
	13	M	R	Gone	No change	Not reported	Gone
	12	M	L	Improved	Worse	Not reported	No change
	4	F	L	Gone	No change	Not reported	Gone
	8	M	L	Gone	No change	Not reported	Gone
	9	F	R	Gone	No change	Not reported	Gone
Fleischacker (1954)	12	M	L	Improved	Worse	Not reported	Improved
	13	M	R	Gone	Improved	Not reported	Improved
	12	M	L	Improved	No change	Not reported	No change
Uecker (1954)	13	F	?	Not reported	Not reported	No change	Improved
	13	M	?	Improved	Not reported	No change	Improved
	15	M	?	Gone	Not reported	No change	Not reported
Munz & Tolor (1955)	14	F	L	Gone	No change	No change	Gone

Of the 29 hemispherectomized children, one or 3 per cent died. This occurred to a 2-year-old male and is reported by Krynauw.[19] His condition is said to have given no cause for alarm during surgery. He became very restless while returning to the ward and suddenly collapsed and died. Thus, the mortality rate as a function of surgery is seemingly low.

TABLE II. AGE DISTRIBUTION OF ALL CASES REPORTED IN THE LITERATURE

AGE DISTRIBUTION	N	%
<1 year	1	4
2 years	2	7
3 years	1	4
4 years	4	14
5 years	0	0
6 years	0	0
7 years	1	4
8 years	1	4
9 years	3	10
10 years	1	4
11 years	1	4
12 years	3	10
13 years	5	17
14 years	2	7
15 years	2	7
16 years	0	0
No age reported	1	4

Table II indicates that the cases reported in the literature are drawn from all age groups except years 5 and 6. When the sample is categorized into preschool (ages from birth to 6 years), middle childhood (ages 7 to 12 years) and adolescence (ages 13 to 16 years) we find little difference between the number included in each developmental category. For 27 reported ages, 30 per cent come from the preschool group, 37 per cent from the middle childhood group, and 33 per cent from the early to middle adolescent period.

According to Tables III and IV, boys underwent hemispherectomy more often than girls, and the left hemisphere was reportedly removed more frequently than the right one. The sex differences may not necessarily be significant since these differences are relatively small. There does, however, appear to be a greater proclivity for the left hemisphere to be removed. More than half of the cases consisted of the removal of the left hemisphere. Of the 26 cases in which the particular hemisphere removed is indicated, 19 or 65 per cent referred to the removal of the left hemisphere. Ten per cent failed to indicate which hemisphere was removed.

TABLE III. SEX DISTRIBUTION OF ALL CASES REPORTED IN THE LITERATURE

	N	%
Boys	17	59
Girls	12	41

TABLE IV. HEMISPHERE REMOVED

HEMISPHERE REMOVED	N	%	(% OF REPORTED CASES) N = 26
Left	17	58	65
Right	9	32	35
Not reported	3	10	

TABLE V. THE STATUS OF CONVULSIVE SEIZURES FOLLOWING SURGERY

STATUS OF CONVULSIVE SEIZURES	N	%	(% OF REPORTED CASES) N = 20
Completely gone	15	52.0	75
Improved	5	17.0	25
No change	0	0.0	
Absent before surgery	1	3.5	
No data reported	7	24.0	
Expired	1	3.5	

Table V indicates that a major consequence of hemispherectomy is the absence or reduction of convulsions. While close to one fourth of the reported cases did not deal with the pre- and poststatus of convulsions, of the

20 cases which did deal with this variable, 75 per cent no longer experience convulsions, and 25 per cent are improved in that the frequency and/or intensity of the convulsions have diminished. This is one very positive finding. Of the three presenting complaints usually considered as the criteria for hemispherectomy, one may very well be able to predict that convulsions will become extinct or at least become greatly reduced in severity in all or at least in the majority of cases.

A second criteria for hemispherectomy, hemiplegia, is more difficult to assess. Investigators focus on different aspects and with more or less specificity. When the findings are categorized in a general way according to improved, no change in status, or condition worse following hemispherectomy, the results are less fortunate than is the case with convulsions. Table VI indicates that of the 23 cases in which this variable is considered, 35 per cent showed some form of improvement. This varied behaviorally from improved balance to decreased spasticity of the affected limbs. Fifty-two per cent did not show any change, and 13 per cent became worse. The hemiplegia became worse in two cases reported by McKissock.[23] He states, "[Cases Nos. 2 and 7] suffered as a result of operation: both of these were errors of judgment on my part. One developed an increase in hemiplegia which has fortunately been offset by disappearance of the severe behavior disorder, whilst the other has acquired an increased speech defect. This latter case should have been subjected only to a local excision of abnormal parietal cortex rather than to ablation of the hemisphere." Thus, while occasionally one can expect worsening of the hemiplegia, in 87 per cent of the cases the patients were no worse off and some (35 per cent) improved.

TABLE VI. THE STATUS OF THE HEMIPLEGIA FOLLOWING SURGERY

STATUS OF HEMIPLEGIA	N	%	(% OF REPORTED CASES) N = 23
Improved	8	28	35
No change	12	41	52
Condition worse	3	10	13
No data reported	5	17	
Expired	1	4	
	29		

The third criteria, emotional outbursts, also diminish to a great extent. Table VII indicates that of 24 cases in which severe emotional outbursts are reported prior to surgery, 21 or 87 per cent show improvement in this area. Only 13 per cent of the reported cases indicate no change in behavior. In no case did this behavior become worse. It would seem then that along with control of convulsions, one can anticipate effective control of emotional outbursts.

TABLE VII. CONTROL OF EMOTIONAL OUTBURSTS

STATUS	N	%	(% OF REPORTED CASES) N = 24
Improved	21	72	87
No change	3	10	13
Worse	0	0	
None present prior to surgery	1	4	
No data reported	3	10	
Expired	1	4	

Little systematic attention has been given to the actual measurement of intellectual functions. While the consensus of opinion seems to be that intellectual functioning improves as a result of hemispherectomy, few studies[13, 22, 25] have actually reported objective measurements. Table VIII indicates that no data were reported with respect to intellectual functioning for 58 per cent of the cases. While close to one fourth report improvement, 86 per cent of these are based upon subjective evaluations. Of the 14 per cent who report no change in intellectual functioning, only 50 per cent are based upon subjective evaluations—the other 50 per cent being based upon objective measurements. Assessing this variable is extremely complex. No one can measure intelligence per se but only the functions of intelligence as manifested in behavior. What is being measured is intellectual functioning and not native intelligence. The latter is inferred; the former is observed and ascertained through standardized and objective measures. The appraisal of intellectual functioning is further complicated by the numerous factors which alter one's level of functioning. Some of the more important factors are: the ability to see and hear; level of motivation including the desire to cooperate and do as well as one is able; and adequate control of impulses. Howells and Kay[28] state:

TABLE VIII. THE STATUS OF INTELLECTUAL FUNCTIONING FOLLOWING SURGERY

STATUS OF INTELLECTUAL FUNCTIONING	N	%	NUMBER BASED UPON IMPRESSION	NUMBER BASED UPON OBJECTIVE MEASUREMENTS
Improved	7	24	6	1
No change	4	14	2	2
Worse	0	0	0	0
No data reported	17	58		
Expired	1	4		

> In our experience in testing cases of infantile hemiplegia before operation we have become aware of the difficulties involved in ascertaining reliable and stable indices of the intellectual ability. In particular, we have noted that as well as the child's physical handicap in completing performance tests, his frequent distractibility, memory defects, short lapses of attention, lack of confidence, and perhaps also his often considerable gap in formal education, have lowered his test results to an undetermined extent.

In view of these many variables, one needs to be cautioned against conclusions which infer that native intelligence rather than intellectual functioning becomes or does not become elevated. Krynauw[19] indicates:

> Improvement in the mental sphere presupposes and is dependent upon, the integrity of the remaining hemisphere and its ability to function normally once it has been released from abnormal influences from the pathological side.

It would seem then that once the pathology is removed and the motor "driveness" of the individual restored to a more stable level, intellectual functioning as measured by standardized tests, is able to become more adequately maximized.

DISCUSSION

A review such as this brings to the fore many questions and problems for the researcher in this area. While investigators are idiosyncratic in their interests and necessarily focus on different aspects of the problem, there is a need for greater systematization in reporting clinical case accounts if a complete understanding of the hemispherectomized patient is to be achieved. This discussion will consider the ways in which investigators can communicate and make their findings more meaningful to others as well as present suggestions for future research. It would seem that all investigators should report their face sheet data, i.e., a patient's age, color, religion, socioeconomic level, etc. Furthermore, one would need to consider dominance, presenting symptoms, the specific time in the total course of study when certain observations are made, and the particular hemisphere removed. These data are available to all and should be reported if systematic comparisons are to be made between investigators. If a follow-up study is done one would also need to indicate the sources from which particular data stem and the time factor in relation to the date of hemispherectomy. Thus, it is important to indicate whether the investigator is reporting his own observations based on specific tests or is reporting anecdotal material related by the patient's family. One would also need to indicate whether the observations are made while the patient still resides in the hospital or as an outpatient. There is also a tendency to speak collectively of drugs rather than to specify particular drugs and dosage. It is insufficient to indicate that a patient no longer has seizures following hemispherectomy. One also needs to spell out to what extent this is evident when the patient is maintained on anticonvulsive drugs and to what extent this is so when the patient is free of drugs. There are also investigators who describe in a general manner that a child has emotional outbursts, but there are no indications as to what situations instigate the outbursts and just what the outbursts entail. Also, quantitative measurements should be utilized whenever possible. It was pointed out earlier that subjective evaluations are made regarding intellectual functioning and also regarding the appraisal of social and emotional development and adjustment. This is unfortunate since there are tools available[29, 30] which can quantitatively measure changes in specific intellectual functions such as general fund of information, comprehension, arithmetical reasoning, immediate recall, vocabulary, planning ability, perceptual skills, visual-motor coordination and integration, and ability to handle abstract ideas. In like manner, there are scales which can measure social development,[31] and projective techniques[32, 33, 34] which can measure specific personality variables such as hostility and aggressivity, ability to relate to others, needs and need systems, self-concept, etc. Thus, if one is to follow a pre- and postoperative research design, one must be very specific regarding the sample used, the time of observation, as well as the sources and tools of observation. Measurement per se is not invariably more useful than description. Descriptions have a very definite place; however, if descriptions are to be useful, they must elucidate very clearly and specifically that which is being observed. It is only in this way that one investigator can directly compare his findings with that of another investigator. A great deal of emphasis has been placed in this discussion on the importance of indicating the time when particular observations are made. Research upon the hemispherectomized patient necessarily entails a longitudinal kind of research design. Unless the time factor is clearly specified, cross validation becomes especially difficult.

One can certainly question the validity of the findings reported in this paper since the emphasis and interests of the investigators proved to be so varied. While this is true, there were nevertheless consistent findings even for so varied a group. Thus, epileptic seizures were greatly reduced in all of the studies regardless of the investigator. This was also true regarding emotional outbursts. While the findings reported here may be considered general, they nevertheless emphasize the need for more specific and systematized research.

There are several ideas which come to mind at this time regarding suggestions for future research. Since hemispherectomy has been extended to all age levels it would be interesting to investigate to what extent the prognosis differs from one age level to another when the presenting complaints are similar—hemiplegia, intractable seizures, emotional outbursts, and mental retardation. When the present data were analyzed for three age levels (preschool, middle childhood, and adolescence), it was found that there were no differences in the consequences of hemispherectomy in so far as status of seizures, status of hemiplegia, and status of emotional outbursts are concerned. These must be considered fairly tentative findings since tests of statistical significance could not be applied due to the many zero cells and the relatively small number of cases. In like manner, consequences of surgery can be systematically evaluated for sex differences, dominance, and the particular hemisphere removed. It was reported that there was a greater tendency for the left hemisphere to be removed than the right. This finding in and of itself is meaningless but does raise questions which can be pursued if enough systematic data are available. To those who feel that hemispherectomy greatly improved intellectual functioning, one could certainly study and evaluate the cases where this occurs and those where this does not occur. With the aid of objective measurements, one could even determine how much or how little change occurs. A study also needs to be done with regard to those cases whose hemiplegia improves and those who do not improve.

Medicine has become a comprehensive field in that it is becoming more and more concerned with the treatment of the total person. Thus, the pediatrician is concerned with the illness of the patient but is also becoming concerned with the patient's reaction and adjustment to his illness. We are beginning to see more and more the need for guidance in the treatment of patients who have undergone hemispherectomy. Their entire way of life needs to be restructured, relearned, and new goals established. This can be done only with the aid of the physician who is treating the patient. In the case of the child who is undergoing hemispherectomy, both the pediatrician and the neurosurgeon need to understand the total consequences of surgery—social, economic, and medical if he is to help bring about an effective adjustment for the child and his family. Research in this area will need to be interdisciplinary and findings pooled, since pediatrician, neurosurgeon, neurologist, psychologist, and psychiatrist each contribute to the total understanding of the patient. So long as each specialty works independently, a total Gestalt will be lacking. Systematized and well-controlled interdisciplinary research will no doubt prove to be more fruitful in the end.

CONCLUSIONS

What information then can the pediatrician and neurosurgeon impart to the parents of hemiplegic children who are being considered for hemispherectomy? It would seem that he could point out that research findings dealing with children tend to indicate a low surgical mortality rate, a very good chance that intractible seizures will become extinct or greatly reduced in number and severity, and more adequate control of emotional outbursts. The prognosis of the hemiplegia itself is indeterminant at this time although some do improve. While mental retardation is certainly not cured by hemispherectomy, it seems reasonable to suppose that more optimal intellectual functioning will ensue if the hypertonic behavior of the individual prior to surgery interfered with the efficacy of his intellectual functioning and is absent following surgery.

SUMMARY

This paper reviews the British and American literature regarding the application of hemispherectomy to children suffering from infantile hemiplegia, intractable seizures, emotional outbursts, and mental retardation. While investigators differ in the amount and kind of information they report, certain trends are evident when the 29 cases are evaluated in terms of consequences of surgery. There seems to be a low surgical mortality rate, decrease or extinction of seizures, more effective control of emotional outbursts, and, in some cases, improvement in the hemiplegia itself.

Consideration is given to ways in which research in this area can be made more systematic and more adequately communicated. Suggestions for future research are also presented.

The author wishes to express his gratitude to Dr. Robert B. King, assistant professor of neurosurgery, Washington University School of Medicine—*now professor and head of the department of neurosurgery, Syracuse Upstate Medical Center*—for introducing him *to this area of study.*

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Comments on Current Literature

HYPOPHOSPHATASIA

The association between deficient bone formation and low alkaline phosphatase activity in the serum and tissues was first recognized as such by Rathbun[1] in 1948. Various clinical aspects of the condition, called hypophosphatasia by Rathbun, had been recorded earlier. Subsequent reports, some of which used the terminology, low phosphatase rickets, indicated that this bone disorder is more common than was suggested originally. At the present time a clearer concept of hypophosphatasia as a disease state is emerging, particularly with reference to its differentiation from vitamin D resistant rickets, and from osteogenesis imperfecta, both of which may be accompanied by changes in the teeth. Rathbun's original case was that of a male infant, seen first at 3 weeks of age, who was admitted to the hospital because of failure to gain weight and apparent pain on handling. In this young infant, defective mineralization of the skeleton was quite evident, with marked rachitic changes in the bones and diminished serum alkaline phosphatase activity. The low level of alkaline phosphatase persisted through six weeks of hospitalization, during which the infant was under vitamin D therapy, supplemented by thyroid and testosterone. At the time of necropsy, diminished alkaline phosphatase activity in the tissues was demonstrated. Pathologic bone lesions were described as indistinguishable from those associated with vitamin D resistant rickets.

Cases reported since 1948 have attested to the wide variability in age of onset in this condition—from birth, to adolescence, to adult life. In one instance reported by McCance and his associates,[2] defective mineralization of the skeleton was suspected before birth by x-ray examination. At birth the infant showed changes in the long bones, a poorly developed bony cranium with widely separated and communicating fontanels, and a flattened chest; beading at the costochondral junctions was noted. An older sibling who died at 14 weeks of age was described as having the same condition. A patient described by Engfeldt and Zetterström,[3] on the other hand, appeared to develop satisfactorily until the age of 3 months, when failure to thrive led to the discovery of a generalized bone disease, which in some respects resembled rickets. Similarly, Sobel and her colleagues[4] reported the case of a well-developed child first seen at 19 months of age. During the two months preceding, several teeth had been shed, and weakness, pain on movement, and deformity of the limbs had become apparent. Onset in still older children has been described.[5, 6] Low levels of alkaline phosphatase activity were noted in two brothers, aged 10 and 13 years, when they were admitted to the hospital for corrective orthopedic procedures.[6] Likewise, cases have been reported in adults of both sexes, in some instances the first sign being premature loss of teeth, or spontaneous fractures, or both.

The *American Journal of Roentgenology* for September, 1957, carried an interesting and well-illustrated article on hypophosphatasia, the purpose of which was "to outline the major features and to draw a more complete picture of the disease."[7] This report by Currarino, Neuhauser, Reyersbach, and Sobel covers a total of 33 cases of the disease from the literature and from information on some unpublished cases. These authors stress the wide variability with age in both the clinical and the roentgenographic features, and present the findings in three age groups: in newborns, with possible detection in utero, in infants, and in children. Tabulation of the patients according to the age at onset of symptoms revealed that in general the severity of the manifestations decreases as the age of onset increases. Prognosis seems to be poor when the disorder is clearly manifest at birth, or in very early neonatal life. In six newborn infants the clinical features of the disease were essentially the same. "Each was born at term with a globular and 'boneless skull,' soft skeleton, and severe deformities of the extremities."[7] These infants either failed to breathe or had severe respiratory difficulty, and five died within the first hour of life. The sixth lived for nineteen days, showing during this time increasing respiratory distress. Three patients, in whom manifestations were apparent soon after birth, died between the ages of 2 and 6 months. While the skeletal abnormalities in these three were somewhat less severe, they were generalized and were undoubtedly present at birth. Common signs and symptoms included failure to gain weight, slow growth in length and in head circumference, irritability, and jerky movements or convulsions. Prominent features in some instances were cyanosis, fever, sudden episodes of loud crying, anorexia, vomiting, and constipation.

In a group of older infants the symptoms appeared gradually between the first and the sixth months of life, and followed a period of apparently normal development. When the disease appeared in infancy, the outstanding features were failure to thrive, with recurring episodes of unexplained fever, anorexia, vomiting, constipation, irritability, and hypotonia. In some of these infants convulsions and cyanosis were noted. Roentgenologic examination reveals poor calcification of the skeleton; cranial sutures are separated, the anterior fontanel is wide and bulging, and often tense. In some cases there is hypercalcemia with the possibility of renal damage. Prognosis is somewhat more hopeful in the older infant; the bones calcify slowly, symptoms tend to abate, and growth proceeds. However, bony deformity persists in varying degrees and may become more marked with time. Craniostenosis may pose a serious problem, necessitating surgery in some cases. These children walk late and are short in stature; they may experience spontaneous fractures. The teeth are hypoplastic and are shed prematurely. Clinically the survivors from this group merge into the third group of patients composed of older children. This third group included patients who came under observation between the seventeenth month and the thirteenth year of life. In a number of instances, mild manifestations could be traced back to early childhood or to infancy. The usual features included delayed walking, defective gait, painful extremities, dental caries, often rampant, and premature loosening and loss of teeth.

Laboratory findings in hypophosphatasia are not considered abnormal except for the uniformly diminished alkaline phosphatase activity and, in some cases, elevation of serum calcium. One interesting finding, however, is the occurrence in the urine of unusually large amounts of a phosphate ester, phosphoethanolamine.[7, 8] This ester is widely distributed in the cells of many tissues of the body. While the metabolic role of this substance is not clear, the suggestion has been made that its presence in the urine of patients deficient in tissue alkaline phosphatase activity reflects a disturbance in the functioning of at least one enzyme system.[9]

Therapy in hypophosphatasia has not been satisfactory in general; trials with growth hormone, vitamin C, thiamine, thyroid, and testosterone have not resulted in significant alteration in the clinical evidence of the disease, or in permanent change in phosphatase activity. The use of testosterone is discouraged since in experimental animals a reduction in kidney alkaline phosphatase resulted from its use. While vitamin D in high doses may accelerate mineral deposition, the dangers of hypervitaminosis in the presence of hypercalcemia and kidney damage must be taken into consideration. A recent preliminary report[10] from Canada describing the use of cortisone in a female infant with hypophosphatasia suggests a remission of many of the pathologic features of the disease, but these findings have not been evaluated completely as yet. Studies in rats of the effect of cortisone on serum alkaline phosphatase activity are likewise in the preliminary stage.[11]

On the basis of the more fully investigated patients included in their survey, particularly the roentgenographic and pathologic studies in the different age groups, Neuhauser, Sobel, and their associates[7] conclude that hypophosphatasia is a definite disease entity "quite unlike any other bone disease." Some features resemble those of rickets, of resistant rickets, or of osteogenesis imperfecta, the manifestations varying with age. "Interpretation of the pathogenesis of the disease has been focused principally on the low phosphatase of the serum, bones and other tissues." The discovery of low phosphatase activity in parents or siblings suggests genetotrophic disease, and manifestations at birth or before indicate that the condition may be congenital. Two genetic explanations have been considered possible: the operation of a dominant factor which is intensified in the homozygous state, but expressed in varying degree in the heterozygous individual; or based on a recessive factor which in the heterozygous state is incompletely covered by a normal gene, so that carriers can be detected. In traits having to do with complex enzyme systems, it is more likely that a number of hereditary factors is involved. Physiologic aspects of alkaline phosphatase and its substrates have been studied with reference to bone metabolism.[2, 8, 9] The abnormal metabolite, phosphoethanolamine, has been found in the plasma as well as in the urine of patients with hypophosphatasia. In a very interesting and informative review of the biochemical aspects,[9] one author suggests that a study of such conditions as hypophosphatasia may open the way to a better understanding of many enzyme systems of the body.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I have read Dr. Tabrah's gloomy discussion of pediatric practice in the December issue with interest, but with no alarm for the future of pediatrics or pediatricians. I think I can understand what he means, although I do not agree with most of what he says. There is no trade, profession, occupation, or business that does not have its disadvantages and moments of boredom, be it burglary, tight-rope walking, preaching, or banking—or even professoring in a large teaching hospital where unusual cases abound, of which Dr. Tabrah seems to be so fond.

There can be no doubt that pediatric practice sometimes approaches the point where the pediatrician wonders if he will ever see anything again except run-of-the-mill colds, inoculations, and ''checkups.'' He certainly will, and if he has been in practice for any length of time and goes over his records, he finds that he has seen about every disease that children have.

Pediatrics will continue to be a legitimate specialty because, although the pediatrician is the child's family doctor, and is in this sense a general practitioner, innumerable problems arise which are not seen in the adult, for the child is not merely a small man. He is a different *sort* of man, with his own private and particular troubles, many of which need, in order to be dealt with successfully, special knowledge which the general practitioner does not have. I fail to see how Dr. Tabrah can think that the practice of pediatrics is narrow, or that general practice will furnish more interesting problems.

It is true, as he has said, that the pediatrician has to see a large number of patients each day in order to make a good living. This won't hurt him; so does every other doctor except a surgeon. The practice of medicine has never been an *easy* way to make a living. There is, however, one great disadvantage in the pediatrician's life, from which he suffers more than any other doctor—the telephone. He is at the mercy twenty-four hours a day of as many women as comprise his clientele; he is continually interrupted at whatever he may be doing to talk of things which often amount to nothing. But life can't be all cakes and ale, no matter how one earns his living, and there really is not too much else in the pediatrician's business that incommodes him a great deal.

Dr. Tabrah says: ''A few years ago this colorless job [the practice of pediatrics] was relieved by challenges of frequent and severe disease, and the physician was called upon to use his greatest ingenuity.'' To most people there is certainly nothing ''colorless'' about children, and it has always seemed to me that a pediatrician has to use a pretty considerable amount of ingenuity and wit every day of his life, whether or not he is dealing with serious diseases. Dr. Tabrah seems to think that there is satisfaction only in dealing with unusual cases, or in being shut up within the ivory towers of a big teaching hospital. This is not so for most people, and I can assure him from a long experience in a big teaching hospital, and also as a plain ''house-to-house'' doctor, that there is as much tiresome routine in a teaching hospital as there is in the ''outside'' practice of pediatrics.

I agree with Dr. Tabrah that some men are unfitted for pediatric practice because of individual tastes and personalities: this is not unnatural; there are plenty of young men in all occupations who get into the wrong job.

I know well at present two relatively young men who practiced pediatrics for a while—didn't like it—and are now working in research laboratories in a big hospital where they have both already done outstanding work, and will undoubtedly accomplish much more before they are done. Each has found his proper place. The practice of pediatrics was not it.

If a man does not have a great liking for children, it is best that he keep out of pediatrics. This may be Dr. Tabrah's trouble. To most pediatricians there is something about a child that is appealing in the highest degree. I think that most of us have not just a *liking* for children, but a genuine love for them—for their freshness, their simplicity, their sheer beauty, their helplessness. Is there anyone more deserving of help than a child in trouble? Can a man occupy himself better than in trying to get him out of it? I doubt it.

LEWIS WEBB HILL

BOSTON, MASS.

News and Notes

Fellowships in developmental diagnosis are available at the **Clinic of Child Development** which is sponsored jointly by the Department of Pediatrics of the Ohio State University, College of Medicine, the Children's Hospital of Columbus, Ohio, and the State Department of Mental Hygiene and Correction. The Clinic is concerned with the evaluation of neurologic status and maturity level in children in the preschool period suspected of having deviations in development. The majority of the children have neuropsychiatric disabilities which are organic in nature. In addition to diagnostic evaluation, guidance in the management of problems, and help in securing the necessary medical and community services is provided.

Fellowships are open to pediatricians, or psychiatrists who are board eligible. They are for a period of one year beginning July 1, 1958, with one position each six months available, and carry a stipend of $5,000. Physicians who are trained will have opportunities to engage in research projects designed to elucidate the etiologies of the neuropsychiatric disabilities of childhood and to enter into the teaching program.

Address inquiries to: Dr. Earl H. Baxter, Chairman, the Department of Pediatrics, The Ohio State University, or to Dr. Hilda Knobloch, Director of the Clinic of Child Development, at the Children's Hospital, 561 South 17th Street, Columbus 5, Ohio.

Dr. Harris D. Riley, Jr., has been appointed chairman of the department of pediatrics at the University of Oklahoma School of Medicine, Oklahoma City. Dr. Riley was formerly on the staff of the pediatric department at Vanderbilt University School of Medicine.

The *Summer Camp for Diabetic Children* will be conducted for the tenth year under the auspices of the **Chicago Diabetes Association**, July 20–August 10, at Holiday Home, Lake Geneva, Wis. Boys and girls 8-14 years of age are eligible.

As in previous years, the camp will be staffed by resident physicians, a nurse, two dietitians, and a laboratory technician, in addition to the regular counseling and domestic staff of Holiday Home.

Rates for Summer Camp are arranged in accordance with individual circumstances. Applications may be obtained from, and inquiries should be addressed to: The Chicago Diabetes Association, 5 South Wabash Avenue, Chicago 3, Ill. (ANdover 3-1861.)

Applications for the residency from Jan. 1, 1959, to Dec. 31, 1959, in Pediatric Oncology at **Memorial Center for Cancer and Allied Diseases** in New York will be received up to July 1, 1958. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary: $4300 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

The **IX International Congress of Paediatrics** will be held in Montreal, Canada, from July 19-25, 1959, under the auspices of the International Paediatric Association at the invitation of the Government of Canada and the Canadian Paediatric Society. The scientific program has been planned to embrace the problems of child care in their broadest sense, and will include plenary sessions, panel discussions, original communications, and scientific exhibits. Simultaneous interpretation will be employed for all plenary sessions. Official languages will be English, French, and Spanish. A varied program of social events will be offered. The Preliminary Program and registration forms will be distributed in a few months' time to paediatricians throughout the world.

Medical Education Week, with the purpose of focusing the attention on, and informing the public of, the basic significance of medical education, will be held the week of April 20 to 26, 1958.

The **Seventh Annual Clifford D. Sweet Seminar,** sponsored by Children's Hospital of the East Bay, will be held on May 16 and 17, 1958, at the Claremont Hotel in Berkeley, Calif. Guest speakers will be: James G. Hughes, M.D., Professor of Pediatrics and Chairman of the Department of Pediatrics, University of Tennessee Medical School, and Paul H. Holinger, M.D., Professor Broncho-Esophagology, University of Illinois and Children's Memorial Hospital.

Books

The Normal Child. Ronald S. Illingsworth, M.D., F.R.C.P., Second Edition, Boston, Little, Brown & Company, 1957, 356 pages. Price $7.00.

As a general rule, reviews of second editions are limited to pointing out important changes. We are under the impression that this text, by the Professor of Child Health at the University of Sheffield, is not well enough known to practitioners, in the United States at least, although the fact that the first edition, published in 1953, had to be reprinted the following year testifies to its general acceptance. This second edition, moreover, has been completely rewritten and extended in scope to cover the first five years. It is rather a unique book, and we are not familiar with any other text that covers quite the same ground, or has the same purpose. Some quotations from the preface of the first edition describe the author's approach and the scope of the text.

> "In some teaching schools there is too much emphasis on the rare and 'interesting' and too little emphasis on the common conditions which form the large bulk of family practice. In the case of children, many of these common conditions consist of variations from the normal which hardly amount to disease, but which cause a great deal of anxiety to the parents. The doctor may leave the medical school ill-equipped to deal with them." "It is because I felt this knowledge of the normal is not easy to acquire from the available text books that this one was planned." "In planning the book I was constantly faced with the difficulty of deciding what is normal and what is abnormal, and what, therefore, should be included in the book and what excluded It is almost impossible to define the normal. It is certainly not synonymous with the average A child may differ very widely from the average child in physical and mental development and yet be perfectly normal." "Behaviour problems are included in the book because every normal child has them. I feel that a child with no behaviour problems would be highly abnormal."

The author has very ably accomplished the task he undertook. He has arranged his material in four sections: Feeding Problems; Physical Problems; Developmental Problems; and Behaviour Problems (parental attitudes, discipline, sleep, anorexia, crying, etc.). There are a number of more extensive texts on each of these subjects, but by bringing them together in this way in relation to the normal child, a practical book which should be of great value to the practitioner has resulted. The book also is very well written and the discussions make interesting reading. The author shows a wide knowledge of the work and opinions of others concerning the topics discussed, and there is a bibliography running to 468 references. These, however, are not simply quotations but are woven into the discussions based on Dr. Illingsworth's experience.

The text should be of particular value and service to the younger pediatricians starting practice, as most of the problems he will encounter so frequently in pediatric practice, outside of the management of illnesses, are included. The book was of particular interest to the reviewer in connection with the recent criticism of the pediatrician as not being prepared by his training for the problems he will meet in practice and thus finding pediatric practice "unrewarding," which has been the subject of considerable discussion in the JOURNAL in recent months. From this viewpoint alone, the book can be read with great profit by the hospital residents planning to enter practice, as well as by their teachers. It is highly recommended for the practitioner's library.

B. S. V.

Tuberculosis: Every Physician's Problem. J. Arthur Myers, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 290 pages.

Rarely has an author been able to cover a subject of so wide a scope, as concisely and yet as completely, as has Dr. Myers in this splendid work on tuberculosis. The book is divided into three parts. The first includes a brief but comprehensive historical sketch, a discussion of the bacteriologic characteristics of the tubercle bacillus, and a description of the invasion and pathogenesis of primary tuberculosis. In the second part a thorough discussion of the clinical (reinfection) type of tuberculosis is given, including its pathogenesis, diagnosis, and present methods of treatment. An excellent evaluation of the specific drugs presently in use is given in this section. The third part of the book deals with control to eradication, in which, after a brief consideration of the many anachronisms that were once somewhat widespread and have since been abandoned, a careful evaluation is made of the control measures that have been used. The role of the physician in the program for control and eradication of the disease is thoroughly discussed. Finally, the author cautions against the danger of overconfidence, built up by the somewhat phenomenal gains that have been made, and warns that a lessening of the intensity of the present efforts toward control and eradication of the disease could easily result in wiping out all of the beneficial progress made thus far.

The book gives a complete account of present-day knowledge of the disease and its treatment today and should be of interest to every practicing physician, regardless of his specialty.

D. S.

Practical Allergy. M. Coleman Harris and Norman Shure, Philadelphia, 1957, F. A. Davis Company, 471 pages.

Concise, well written, and well printed, this textbook will be of help to any physician, but of the greatest usefulness to the one who has had little or no training in the care of allergic patients. It should also provide an excellent introductory work for medical students. The text is readable. The views expressed are sound. Controversial issues are well handled. The importance of individualizing each case is emphasized.

The pollen chart for the United States may be a little awkward to use. The plant pictures are good, but the list is not complete for some parts of the country. The investigation of environmental factors is well presented but the procedures of environmental control are not.

Many pediatric allergists would object to giving cod-liver oil to allergic infants as the authors recommend and would prescribe instead the crystalline form of the vitamins A and D.

Consideration should be given to the type of infecting organism before prescribing antibiotics to the patient having asthmatic bronchitis.

The authors are to be commended for their very sane presentation of the use of steroid medication.

The book, as its name implies, is concerned with the practical aspects rather than the theoretic aspects of allergic disease. It contains enough of pediatric interest and importance to recommend its use by any practicing pediatrician.

G. B. L.

Barbara. A Prologue. Willard Abraham, New York, 1958, Rinehart & Co., Inc., 94 pages. Price $2.00.

One of Those. Sophia Gant, New York, 1957, Pagent Press, Inc., 88 pages. Price $2.50.

These are two small books for lay reading, by parents to whom children with mongolian idiocy were born, published within a few weeks of one another. Except for the subject they have nothing in common. The author of *Barbara* is a professor of education at a southwestern state university and by the irony of fate was particularly interested in exceptional children. The infant was placed in an institution for retarded children and lived a relatively short time. It is very well written and the story is one of the emotional reactions of the parents following the birth of the infant and their adjustment to the calamity.

It is not so easy to review Mrs. Gant's book. In this case the child, now around 20 years of age, obviously belongs in the group of mongols with minimum retardation. His mother, a former teacher, has devoted her life to his education with remarkable results. A printed sample of a week's schedule or "time table" at grade 7 is amazing. The book is a revelation of what a devoted, never discouraged mother, acting as a teacher, can do. The difficulty in reviewing the book objectively lies in the fact that Mrs. Gant is a deeply religious woman and attributes all of her son's progress and development as God's answers to her prayers, and never in any way to her own work. The book is replete with biblical references on almost every page. Far be it from the reviewer to enter into a discussion of the reasons for the boy's progress. She has accomplished a remarkable achievement and is entitled to her viewpoint and opinion.

B. S. V.

Child Psychiatry. A Thoroughly Reliable Guide to Children's Behavior Problems, ed. 3. Leo Kanner, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 777 pages. Price $8.50.

The third edition of Kanner's *Child Psychiatry* maintains the high standards set by the earlier editions. Many sections have been extensively rewritten. The new edition can be relied on for the inclusion and critical evaluation of recent advances in child psychiatry.

The book is unique among textbooks. Kanner has thought widely about his field. The treatment of each subject reflects his deliberations. He accepts nothing without first weighing it—and then, if he accepts, he accepts tentatively. Yet the reader does not find himself confused by this way of presentation. Rather it leads to clarification.

Kanner writes easily, at times almost conversationally, often with quiet humor, always with great humanity. Psychiatric terms whose meaning might be obscure to the pediatrician are, in the main, avoided.

For the pediatrician—as well as the child psychiatrist—this book should be invaluable. The field is comprehensively covered and a well-selected bibliography is available at the end of each chapter for those who would go to original sources or who want to dig deeper.

H. B.

Laboratory Applications in Clinical Pediatrics. Irving J. Wolman, M.D., New York, 1957, McGraw-Hill Book Company, Inc., 1019 pages.

This book is a comprehensive summary of laboratory procedures which are useful in the practice of pediatrics. The author reviews the normal values for each test according to age, but does not present any methodology except when this knowledge is necessary for obtaining the proper test sample.

The application of the laboratory procedures are discussed in light of the pathologic physiology of the various diseases. The indexing and organization of the book enable the reader to study the application of a single laboratory test or to determine what procedures should be carried out for accurate evaluation of a certain disease. Frequently, the author summarizes the accepted therapeutic regimes and relates the clinical response to this therapy to the changes in laboratory determinations.

This book is not a laboratory manual, but is a discussion of pathologic physiology as shown by routine laboratory tests. It should be a worth-while addition to the library of all persons and institutions interested in the treatment of infants and children.

M. R. B.

Editor's Column

DO WE NEED A NEW PERSPECTIVE IN INFANT NUTRITION?

HAND in hand with the nutritional scientist, the pediatrician has striven for the betterment of nutritional health in our society. The development of the deficiency concept of disease provided a guiding philosophy for this effort, the discovery of the various essential dietary factors a verification of important hypotheses, modern food technology the implementary tools. This grand coalition of effort—scientific, agricultural, commercial—has in the short span of half a century wrought a nutritional revolution.

Not all societies have participated in this revolution. There is still much concern over the welfare of the millions of starving children inhabiting large sections of the globe. This and other considerations have conspired to preserve the deficiency concept as paramount in the nutritional field. For the most part, our students are taught in terms of minimum requirements. Strenuous efforts are being made to show that a number of diseases of uncertain etiology represent deficiency states. Despite our surfeit of food we are being urged to eat more and more. The casual observer easily gains the impression that our society could be still better fed.

But *medicus, circumspice!* The results of the nutritional revolution are plainly visible. Clear-cut examples of deficiency states are difficult to find for purposes of classroom demonstration. Well-nourished children fill your offices. Malnutrition is no longer a major problem in those areas of our country where good medical care is enjoyed.

Perhaps the time has come for an examination of the following question: In our zeal to prevent nutritional deficiencies in the infant and child population have we actually succeeded in feeding them too much? Sparse though they are, the inferential data pertinent to this question are deserving of consideration.

Nutritional excesses can be harmful. The suggestive relationships between dietary fat and atherosclerosis, and between salt intake and hypertension are attracting the attention of the physician who cares for adults. The health experience of life insurants indicates that an optimal weight exists for the adult, for there is a modest increase in mortality for those who are underweight and a striking increase for the overweight. In the experimental animal the case against overfeeding has been documented for a number of species. Of interest to the pediatrician is the inverse relationship between growth rate and longevity which has been noted in widely divergent species, and many years ago Raymond

Pearl concluded that "the length of life depends inversely on the rate of living."

Overnutrition in the adult is fast assuming the status of a major nutritional problem. Whether obesity in the child constitutes a threat of similar magnitude is a question which cannot be answered on the basis of present evidence. However, Hilde Bruch's observations have shown that the obese child tends to remain overweight in adult life. Despite the lack of precise data on this point, the observations on adults together with the results of animal experiments point to the desirability of reassessing childhood nutrition and current nutritional practice in the modern perspective.

A particularly compelling consideration is to be found in the established trend in the growth performance of infants and children. There is ample evidence that the infant and child of today are growing faster than in previous generations. Standard growth charts need periodic revision, and always in the upward direction. This is not an isolated phenomenon, for it has been recorded by Meredith for this country,, by Tanner and Morant for England, Norway and Germany, and by Ebbs for Canada. Children of all ages, save the newborn, have shown a progressive increase in height and weight in successive generations. Maximum height in the male is attained at an earlier age. Both sexes have shown this change, and all economic groups are involved. During this same period, which covers about a hundred years, there has been a progressively downward trend in menarcheal age, and the age at which the adolescent growth spurt occurs.

The reason for this trend is not known, nor is it known whether it extends back beyond the mid-nineteenth century since systematic observations on human growth rates were not made prior to that time. Possible explanations include the progressive hybridization of the western races and the decline in chronic intercurrent disease. Some have speculated that it is merely a phenomenon of recovery from the ravages of the early phase of the industrial revolution. Observations such as the dips in the secular curve during wartime in Europe and the economic depression and the fact that obese children show advanced stature and maturation strongly suggest that improved nutrition is in part responsible.

The question may now be posed: What is optimum growth? Basic to this consideration is the fact that all human growth data are empirical. On a priori grounds there is no way of deciding whether the child of yesteryear was stunted, or the one of today overgrown and overnourished. Nor can we conclude without further evidence that the observed changes in growth pattern have been wholly beneficial, as many would have us believe.

The requirements for many dietary essentials are geared to growth rate, so the definition of optimum nutrition is bound up with the one above. Despite the valiant efforts of nutritionists it must be admitted that precise information on the matter of minimum requirements is lacking for all but a scant few of the essential constituents of the diet. The tendency has been, on the part of physician and official council alike, to err on the side of recommending too much rather than too little. The gaps in knowledge here have been recently highlighted, for example, by the discovery that children in Ceylon appear to thrive on an intake of calcium considerably below that supposedly necessary for the American child. Outside of certain disease states, we know very little about possible variations among children in their dietary needs.

In view of these uncertainties in our knowledge, should we continue to give concentrated formulas to infants, formulas which supply much more protein, calcium, and calories than the usual breast-fed baby receives? Should we foster the earlier and earlier introduction into the infant diet of solid foods for which there is no proved need? Should we continue to condone among the parents of our patients the attitude that bigger babies are better babies? In the light of recent reports of the deleterious effects of modest increases in vitamin D and vitamin K dosages, should we not take another look at current practices in prophylactic vitamin prescriptions?

At the dawn of modern pediatrics there were many forces at work in the direction of undernutrition. These are still in effect in many areas of the world, but today in our society they have been largely replaced by forces operating to promote overnutrition. The decline in intercurrent chronic disease is one such force. Another is modern food technology: the improved digestibility of modern artificial formulas, the tremendous production of high-quality foods, the speed with which foods can be distributed among our people, and the efficiency with which they are protected against deterioration during storage are all important factors. Highly potent dietary supplements are available in increasing quantity: the commercial production of vitamins has risen 700 fold in the last 17 years, and the annual output can now be measured in tons. Promotional advertising is aimed at increasing the desire for even more food. Overnutrition is easier to achieve than at any time in the past. To a large extent it will be the actions of the pediatrician as observer and counsellor which will determine whether it will constitute a threat to the child of the future.

Gilbert B. Forbes

INFANT FEEDS—HOT OR COLD?

IN THIS issue (page 404) we publish a report that has been of considerable interest to the Editorial Board for a number of reasons. By its publication it should not be assumed that the Journal and the members of the Board advocate discarding the time-honored custom of warming the bottle before offering it to the baby. Dr. Gibson, of Abilene, Texas, whose intellectual curiosity led him to question the importance of strict bed rest for children with minor febrile diseases (J. Pediat. 49:256, 1956) has questioned the importance, or better, perhaps, the necessity, of another time-honored custom. Many pediatricians will recall isolated experiences in their practice where babies have been fed unwarmed bottles without apparent harm. Such an experience led Dr. Gibson to investigate the use of unwarmed feeds by a study conducted in his private practice. Eighty-nine per cent of 150 infants accepted cool or cold formulas, and, in 120 of these followed, development proceeded normally. No harmful effects were noted.

Thus the importance of another time-honored custom has been questioned by an "inquiring mind." One of the reasons for its interest is that it is a study based on material in a private practice, in the way so many advances have been made, of which the work of Mackenzie in cardiology is a brilliant example. Further, it was made without the use of a laboratory, although it raises questions that require laboratory investigation. For example, some laboratory worker may be interested enough to determine by means of a thermocouple the temperature of the cool milk by the time it reaches the stomach, and such questions as to whether a cool feeding influences the secretions and peristalsis: studies we doubt if Dr. Gibson is in a position to carry out.

Another reason for its interest, as one member of the Board who reviewed the manuscript remarked, is that it is a warming refutation of the lack of rewards of the private practice of pediatrics—a subject of much discussion by JOURNAL readers since the publication of the letter by Dr. Tabrah last December. We are quite certain that Dr. Gibson has found the private practice of pediatrics in a small city not only completely rewarding, but of exciting interest. There is an old saying, full of truths, that what a man gets out of anything depends upon what he puts into it.

DIET LISTS

IN Professor Illingsworth's recent book, *The Normal Child*, reviewed elsewhere in this issue by the Editor, a paragraph under the heading, "A little knowledge of nutrition" brought recollections of one of the several episodes in pediatric practice when our zeal ran ahead of our knowledge and experience, as so often has happened in medicine. I refer to the handing out to parents of "diet lists" with elaborate details as to the different foods and the exact amounts to be given to children at each meal. It had its genesis to a large extent in the great interest in malnutrition in children that developed some 40 to 50 years ago. This diagnosis was largely based on finding that a child fell below the average of the weight-height-age tables obtained from the measurements of thousands of children of school and preschool age. If a child was a small percentage below the average, he was classified as "malnourished," and steps must be immediately taken to improve his diet. So diet lists became a vogue and were given much lay and medical publicity. The intent was to instruct parents and make it easy for them to give Johnny three well-balanced meals a day, thus providing sufficient calories in desirable amounts of protein, fat, and carbohydrate to prevent malnutrition.

Everyone got into the act. Pediatricians were considered as neglecting their duties if they did not place tremendous stress on the importance of diet. The manufacturers of prepared foods soon had their nutritionists prepare elaborate and attractive diet lists furnished gratis to the doctors to hand out to parents. (Of course there was a joker—introduced into the breakfast, for example, "2 tablespoons of X's sawdust.") There were many conferences and committee meetings held to discuss diets and diet lists, and what should be included and excluded. I recall one held by the Children's Bureau which was preparing a government "hand out" of diet lists. The subject at the moment was what green vegetables should be included besides spinach, and finally cabbage was reached. One of our distinguished colleagues from Boston spoke up in horror. *"Cabbage!!* cabbage for a child, it's impossible. Who ever heard of giving cabbage to a child!" Then a pediatrician from the southeastern section of the country spoke up quietly, "Well, all I've got to say is that if cabbage is not included in the list most of the children in my part of the country won't get any green vegetables." Cabbage was included.

So with the best of intentions diet lists became a great achievement in the modern pediatrics of that period. On starting private practice in 1919 one of my first steps was to prepare an elaborate set of diet lists for children of different ages to be given to parents, and in which considerable pride was taken.

Then the troubles began. Mothers were led to feel that as it was all very scientific, and that if they did not follow the list to the last detail and if they did not see that every last morsel of the indicated amount was consumed at each feeding, the child's health and growth would be in serious danger. In despair, trying to accomplish the impossible, the mother would try persuasion and bribery, then threats, and finally punishment. Mealtime became a "field day" for behavior, enabling the children to gain attention and get their own way. Perfectly capable mothers were made to feel that they were incompetent and were failures as mothers. The entire life of the family became upset, trying to carry out the children's diets prescribed by their doctor. It did not take long for the pediatricians to wake up to the fact that the most important problem was one of attitudes toward food, rather than the rigid detailing of so much of this and so much of that. The implications of the study of Clara Davis in Brennemann's clinic in Chicago was the final push to reality. Some five years after starting practice, with great benefit to both mothers and children, all the diet sheets in my office were torn up, with the exception of those for special conditions such as obesity and for certain diseases where the diet is an important part of the treatment.

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CLINICAL AND HEMATOLOGICAL ASPECTS OF ACUTE ERYTHROMYELOSIS

STUDIES OF THREE PATIENTS

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BOSTON, MASS.

DI GUGLIELMO described the first case of erythroleukemia in 1917[1] and of pure acute erythromyelosis in 1923.[2] These diseases have in common a fundamental alteration of the erythroid series consisting of: (1) *hyperplasia;* (2) *anaplasia* (arrested maturation at primordial and immature stages); (3) *dysplasia* (alteration of the process of maturation resulting in nuclear and cytoplasmatic abnormalities); and (4) *metaplasia* (the presence and proliferation of erythroid cells at the sites of extramedullary hematopoiesis, as in the liver, spleen, kidney, testis, ovary, pancreas, etc.).

Several cases of DiGuglielmo's disease have been reported in adults and in children.[3-20] In the latter group, however, the differential diagnosis is at times more difficult. In childhood, because of a more labile hematopoietic system, diseases such as hemoglobinopathies, congenital hemolytic anemias, von Jaksch-Hayem-Luzet's anemia, may show an erythremic or erythroleukemic pattern as well.

At the Sixth International Congress of Hematology in 1956, DiGuglielmo reviewed the differential diagnosis of the erythremic diseases.[21] In their classification, many controversial aspects have now been clarified by the concept of myeloproliferative disorders.[22-24] This concept emphasizes the theoretical possibility of multiple involvement of all the bone marrow lines in production (erythro-myelo-megakaryocytic) simultaneously or successively in the majority of hematologic diseases. Thus, schematically, three types of disorders can be distinguished—the pure forms, the mixed forms, and the transient forms. On the basis of these classifications, the following types of erythremic diseases are recognizable (Table I).

The concept of myeloproliferative disorders was helpful in the explanation and assessment of some complex diagnostic problems among the 754

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TABLE I. POLYPHASIC MYELOPROLIFERATIVE DISEASES*

Pure erythromyelosis	→ Pure forms (permanent)				
	→ Polyphasic forms	→ Pure erythromyelosis →	erythroleukemia		
		→ Pure erythromyelosis →	erythroleukemia →	pure leukemia	
		→ Pure erythromyelosis →	erythroleukemia →	pure leukemia →	reticulosis
Erythroleukemia	→ Pure forms (permanent)				
	→ Polyphasic forms	→ Erythroleukemia →	leukemia		
		→ Erythroleukemia →	erythromyelosis		
		→ Erythroleukemia →	leukemia →	myelofibrosis	

*Katsunuma (cited by DiGuglielmo[21]).

cases of acute leukemia in childhood (birth to 16 years) followed in the Tumor Therapy Clinic of The Children's Cancer Research Foundation in Boston (1947 to 1957). Only two instances of pure acute erythromyelosis and one of acute erythroleukemia, however, were found in this large group. Complete clinical and hematological details, together with the pathological findings in these three patients, will be presented and discussed in an attempt to contribute to a better understanding of some of the pathogenic mechanisms of these disorders.

CASE 1

J. P. was a 16-year-old white girl of Italian extraction. The family history was noncontributory. Past history revealed normal birth and development with regular immunizations and no illnesses other than repeated tonsillitis. In August, 1956, she had her first menses, which was neither profuse nor prolonged.

In 1954, following a dental extraction, the patient had alveolar oozing for approximately one month. No bleeding manifestations had been experienced before this episode, and none occurred subsequently until October, 1956, when one of the left lower molars was extracted and she again had an oozing of blood for a few days, with a probable infection at the site of extraction. Following this episode in October, she became increasingly more tired, developed shortness of breath on exertion, and appeared very pale. In the middle of December, 1956, the girl was admitted to an outside hospital where she was found to have a hemoglobin level of 3.9 Gm., red blood cells 960,000, and white blood cells 5,250. The differential was reported as follows: 38 per cent polymorphonuclear leukocytes, 36 per cent lymphocytes, 26 per cent "blast" forms, and numerous erythroblasts. The bone marrow biopsy was reported as consistent with acute leukemia. She received prednisone and three blood transfusions and was then transferred to the Tumor Therapy Clinic of The Children's Cancer Research Foundation on Jan. 4, 1957.

Physical examination showed a pale, slightly jaundiced, well-nourished, and well-developed 16-year-old girl, weighing 46 kilograms. There were no petechiae or ecchymoses. The liver was palpable 3 cm. below the right costal margin, the spleen 5 cm. below the left costal margin. There was generalized moderate shotty lymphadenopathy. The rest of the examination was noncontributory.

The clinical condition was unusually good and the girl was followed on an outpatient basis, with frequent visits. She remained clinically well until the end of March, 1957, when her condition began to deteriorate. She developed a sore throat (*Staphylococcus aureus*) and epistaxis. On April 10 she was admitted to the hospital.

On examination, the weight was 42 kilograms, the temperature 39° C. The skin was hirsute, with facial acne. No ecchymoses or petechiae were seen. There were monilia-like patches over the hypertrophic gums, tongue, and buccal mucosa. Bleeding points were seen along the soft and hard palate, and the tonsils were covered with white confluent patches. The upper gum, along the hard palate, was heavily infiltrated with a necrotic, soft, purulent mass measuring 1.5 by 3 cm. Submaxillary and cervical nodes were massively enlarged. The liver was now palpable 5 cm. below the right costal margin, and the spleen at the left iliac crest. The rest of the examination was noncontributory.

The mass in the oral cavity grew rapidly to involve the buccal mucosa, causing her much pain and preventing her from eating. She had a spiking temperature, up to 41° C. There were no hemorrhagic symptoms. She died quietly on April 21, 1957, three and one-half months after her first visit to the Tumor Therapy Clinic, and about six months after the onset of the disease.

HEMATOLOGIC EVALUATION (CASE 1)

Peripheral Blood (Table II).—The erythroid series showed hypochromic anemia (mean corpuscular

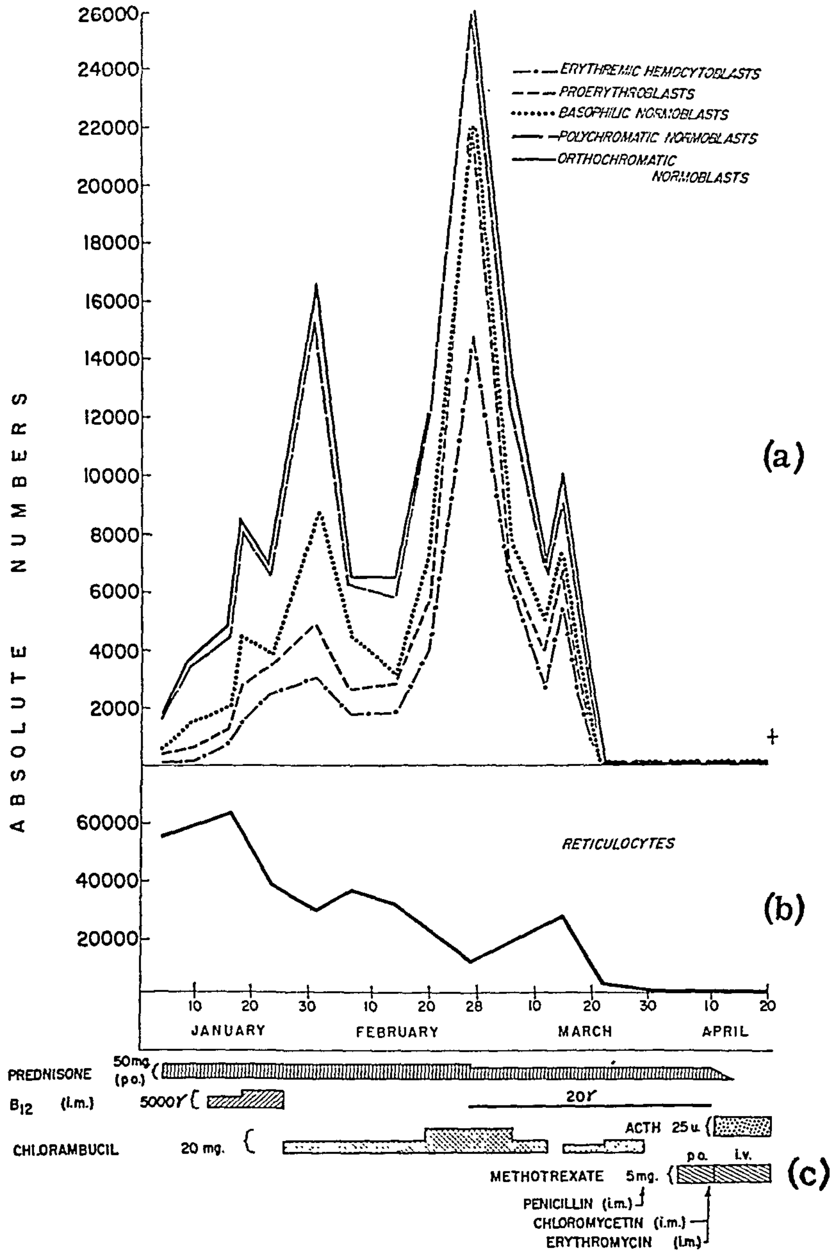

Fig. 1.—Case 1. *a*, Absolute numbers of nucleated red cells. *b*, Reticulocytes in the peripheral blood. *c*, Treatment.

hemaglobin 25.9$\gamma\gamma$), with anisopoikilocytosis. Spherocytes, numerous schizocytes, and polychromatic cells were present, some of which were definitely basophilic while others showed a heavy basophilic stippling. Rouleaux formation was also occasionally observed. At first the reticulocytes were 1.9 per cent, but they decreased progressively to complete disappearance during the course of the disease. Frequent blood transfusions kept the hemoglobin range between 6 and 10 Gm.

The peripheral blood was characterized by: (a) nucleated red cells, and (b) cells difficult to classify ("blasts" in Table II). All types of nucleated red cells were represented (Fig. 1). Many of them showed severe alterations such as karyolysis, severe nucleocytoplasmatic asynchronism of maturation. The percentage of the more immature forms increased during the course of the disease (Fig. 2). Hiatus erythremicus* was noted occasionally. The absolute number went through three main periodic rises with intervals of temporary decreases, each rise being greater than the one preceding. Following the last, a steady decrease to complete disappearance of nucleated red cells was observed. In relation to the total nucleated cells they ranged from 49.2 per cent in the beginning to none at the end.

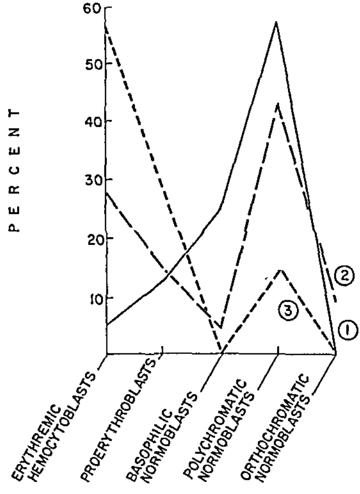

Fig. 2.—Case 1. Samples of the percentual distribution of nucleated red cells in the peripheral blood during the course of the disease.
1, January 9. *2*, February 14. *3*, February 27.

The other cells present (Figs. 3, 4) were usually round in shape, often

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*"Hiatus erythremicus"—many young forms and many mature forms present, but the intermediate forms are missing (Fig. 14). (Compare with hiatus leukemicus of Naegeli.)

TABLE II. CASE 1

DATE	TOTAL NUCLEATED CELLS/MM.^{3}	"BLASTS"*	NUCLEATED RED CELLS/MM.^{3}	WHITE CELLS							
			TOTAL*	TOTAL*	MYELOBLASTS	PROMYELOCYTES	MYELOCYTES	METAMYELOCYTES	MATURE GRANULOCYTES	LYMPHOCYTES	MONOCYTES
Jan. 4	3,100	898 28.9%	1,404 45.3%	798 25.7%	-	-	18 2.2%	-	509 63.7%	254 31.8%	17 2.2%
Jan. 9	7,100	1,369 19.2%	3,500 49.2%	2,231 31.4%	-	17 0.8%	18 0.8%	-	1,530 68.5%	612 27.4%	54 2.4%
Jan. 16	13,700	3,960 28.9%	4,690 34.1%	5,050 36.8%	-	-	100 1.9%	-	3,960 78.4%	900 17.1%	90 1.7%
Jan. 18	21,700	6,600 30.4%	8,220 37.8%	6,880 31.7%	-	-	130 1.9%	-	5,650 82.1%	1,100 15.9%	-
Jan. 23	17,700	5,510 31.3%	6,800 38.2%	5,390 30.5%	110 2.0%	110 2.0%	-	-	4,150 76.9%	870 16.1%	150 2.8%
Jan. 31	47,000	21,060 44.8%	16,500 35.0%	9,440 20.0%	-	-	-	-	8,240 87.2%	600 6.3%	600 6.3%
Feb. 6	28,000	15,090 53.8%	6,450 23.0%	6,460 23.0%	-	-	-	-	6,250 96.7%	210 3.2%	-
Feb. 14	37,200	26,721 71.8%	6,500 17.3%	3,979 10.7%	-	-	-	-	3,670 92.2%	309 7.8%	-
Feb. 20	96,000	75,200 78.3%	12,450 13.0%	8,350 8.7%	-	-	-	-	8,350 100%	-	-
Feb. 27	89,000	51,192 57.5%	25,800 29.0%	12,008 13.4%	-	-	629 5.5%	-	10,750 89.2%	629 5.3%	-
March 6	56,000	34,900 62.3%	13,500 24.2%	7,600 13.5%	-	-	425 5.5%	-	7,175 94.4%	-	-
March 12	26,900	16,900 62.8%	6,950 25.9%	3,050 11.3%	-	-	-	-	2,800 91.8%	250 8.2%	-

March 15	71,000	55,600 78.3%	9,800 13.8%	5,600 7.8%	-	-	-	-	4,300 76.7%	1,300 23.2%	-
March 18	86,000	71,280 82.8%	4,860 5.7%	9,860 11.4%	-	-	-	-	5,680 57.6%	4,180 42.4%	-
March 26	285,000	270,750 95.0%	-	14,250 5.0%	-	-	-	-	8,500 60.7%	5,700 39.3%	-
March 29	294,200	279,490 95.0%	-	14,710 5.0%	-	-	-	-	10,885 74.1%	3,825 26.0%	-
April 1	191,000	183,950 96.3%	-	7,050 3.7%	-	-	-	-	5,140 73.1%	1,910 26.9%	-
April 3	271,000	267,340 98.6%	-	3,660 1.4%	-	-	-	-	3,660 100%	-	-
April 5	322,000	318,780 99.0%	-	3,220 1.0%	-	-	-	-	3,220 100%	-	-
April 8	244,000	237,400 97.4%	-	6,600 2.6%	-	-	-	-	4,880 73.9%	1,720 26.9%	-
April 10	232,000	229,680 99.0%	-	2,320 1.0%	-	-	-	-	1,620 69.9%	700 30.1%	-
April 17	325,000	320,775 98.4%	-	4,225 1.6%	-	-	-	-	4,225 100%	-	-

*Absolute number and percentage of total nucleated cells.

showing small protrusions of the cytoplasm. They presented a marked basophilic cytoplasm, peroxidase stain negative. The nucleus was large, covering three fourths of the cell and presenting a uniformly delicate structure. In some of the elements, however, the nucleus had a "combed-out" appearance. One to four colorless nucleoli were present, not clearly defined. Among these cells many showed a definite halo on the side of the nucleus (initial hemoglobinization?) and they were included in the nucleated red-cell group as hemocytoblasts with erythroid characteristics. The remaining cells were considered in a block ("blasts") as precursor (hemohistioblasts, hemocytoblasts)[5, 7, 25, 26] and abnormal prehemoglobinized erythroid cells (paraerythroblasts of DiGuglielmo).[3, 7, 10, 13] The exact classification of these cells still remains an open question.

The number of these "blasts" steadily increased during the course of the disease (Fig. 5). This increase may be represented by a straight line when the logarithmic value of the cells is plotted against time. The slope of the best interpolating line calculated by the method of the least squares was 0.0222 ± 0.0016. The trend among the various values was found to be highly significant. Coincidental to the administration of a high amount of chlorambucil (0.420 mg. per kilogram per day), temporary interruption of

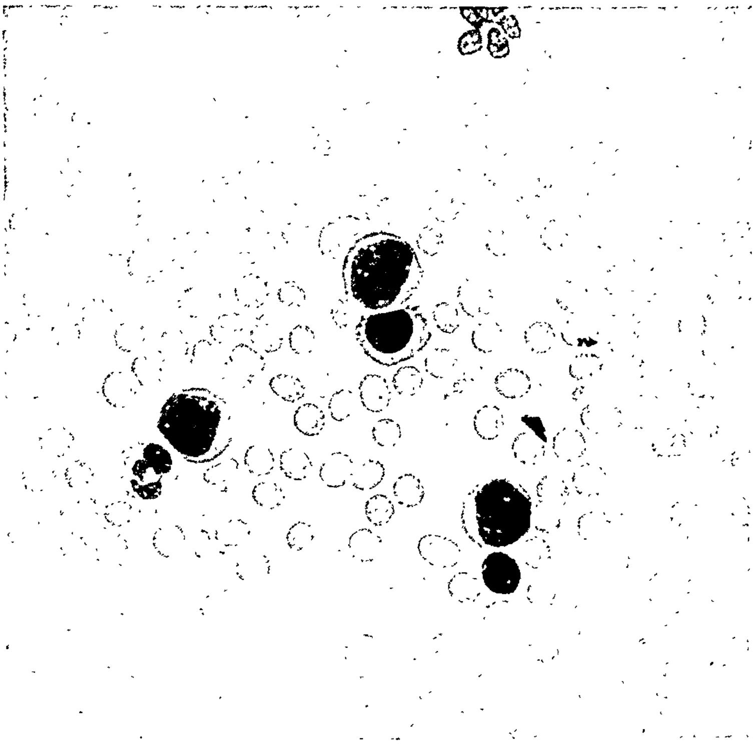

Fig. 3.—Case 1. Photomicrograph of the peripheral blood showing: (a) Presence of nucleated red cells. (b) Alterations of the erythrocytes. (c) Mature multilobulated granulocytes. (d) "Blasts" (see text). (×700.)

the rise in number of these cells was observed.

The myeloid series was mainly represented by extremely mature granulocytes. Their number ranged between 800 and 14,700 per cubic millimeter. These were characterized by multilobulated nuclei, most of them presenting small pediculated buds (Karyoschizes), and lack of the specific neutrophil granulation, the eosinophils and basophils having normal granulation. Correction of this lack of neutrophilic granulation was noted in coincidence with vitamin B_{12} therapy.

Lymphocytes, initially within normal range, were characteristically depressed by the treatment with chlorambucil.[27] Monocytes were occasionally present. *Platelets* averaged around 50,000 per cubic millimeter. Two sudden elevations in the count seem to have been related to discontinuation of therapy (chlorambucil).[27]

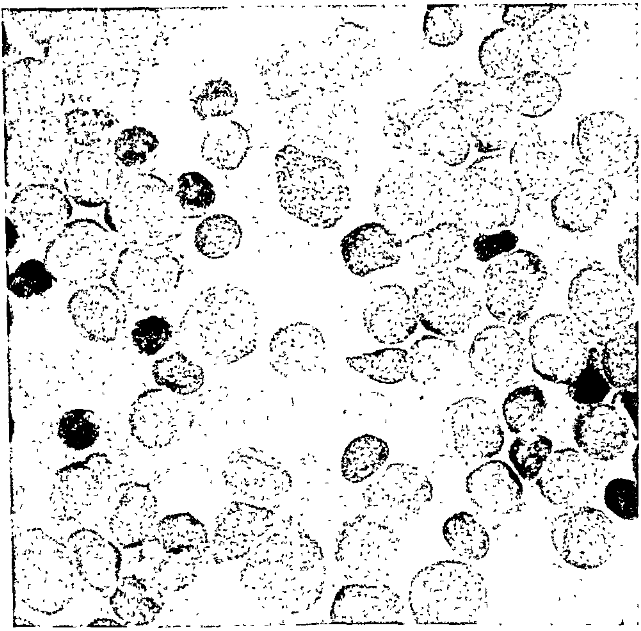

Fig. 4.—Case 1. Photomicrograph of the peripheral blood (sic) showing the marked hypercellularity and the anaplastic types of cells (final stage of the disease).

Tests.—

The blood group O, Rh positive.

The total serum bilirubin on January 4 was 1.5 mg. per cent, free, 0.5 mg. per cent.

On March 29 it was 1.3 mg. per cent, free, 0.2 mg. per cent.

*Serum Iron** determinations were as follows:

January 4	250 γ per cent
January 31	280 γ per cent
February 27	157 γ per cent
March 6	140 γ per cent
March 9	130 γ per cent

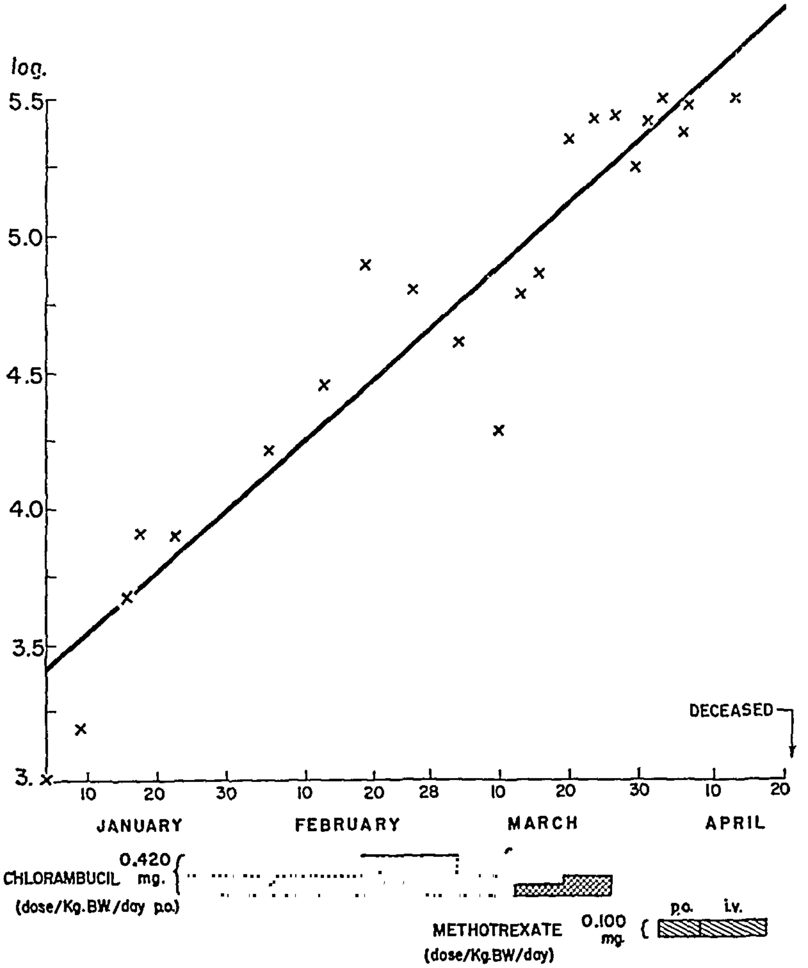

Fig. 5.—Rate of the increase of the "blasts" plus erythroid hemocytoblasts in the peripheral blood. This rate is represented by a straight line in a semilogarithmic system. Ordinate: logarithms of the number of "blasts." Abscissa: time in days.

The Coombs test, direct and indirect, was repeatedly negative.

Electrophoretic migration of protein, lipoprotein, and glycoprotein was within normal limits.

Electrophoretic migration of hemoglobin was normal.

Repeated skeleton surveys and chest x-rays were negative.

Bone Marrow.—

Five bone marrow samples were obtained during the course of the disease by trephine biopsy, aspiration, and curettage. The examination was carried out on the smears, the sections of the clotted sample, and the biopsy,

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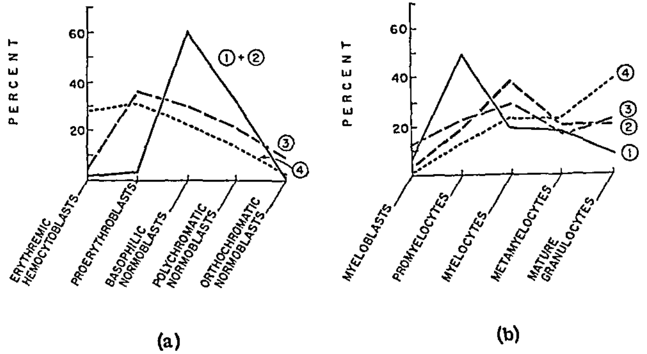
*Normal value of serum iron 90 to 150 gamma per cent.



(a) (b)

Fig. 6.—Case 1. *a*, Maturation curves of the erythroid series in the bone marrow. *b*, Maturation curves of the myeloid series
1, January 10. *2*, January 21 *3*, February 13. *4*, March 15.

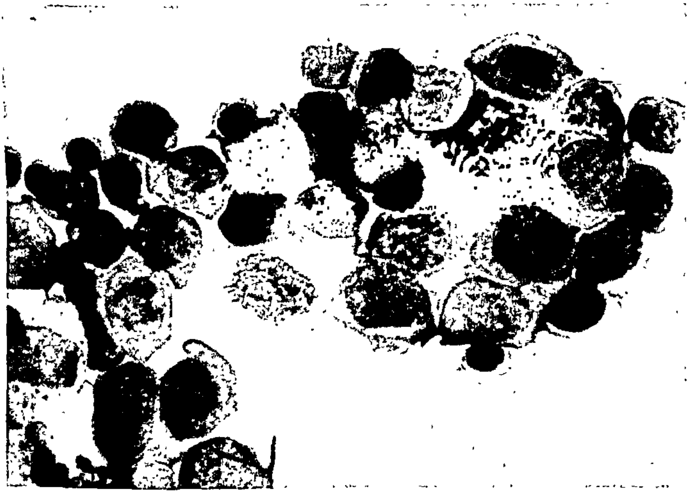


Fig. 7.—Photomicrograph of the bone marrow aspirate showing the typical arrangement of the erythroid cells with the immature elements in the center (one in mitosis) and the maturing one in the periphery. (×850.)

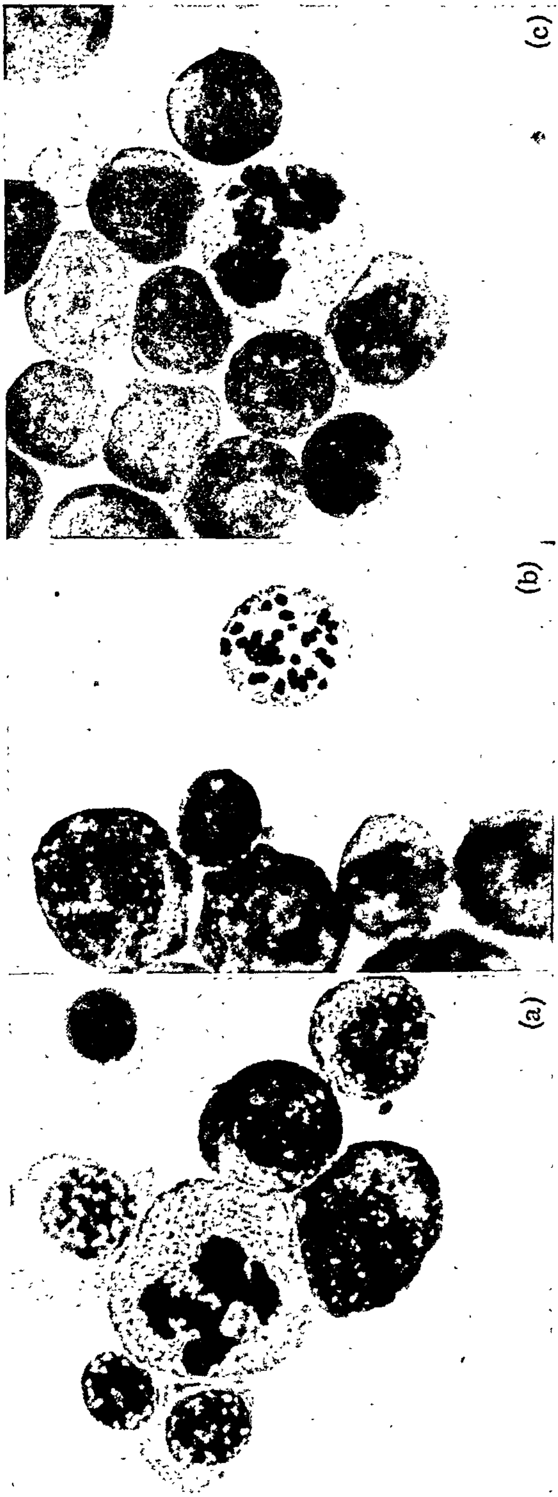


Fig. 8, *a-c.* (*For legend see opposite page.*)

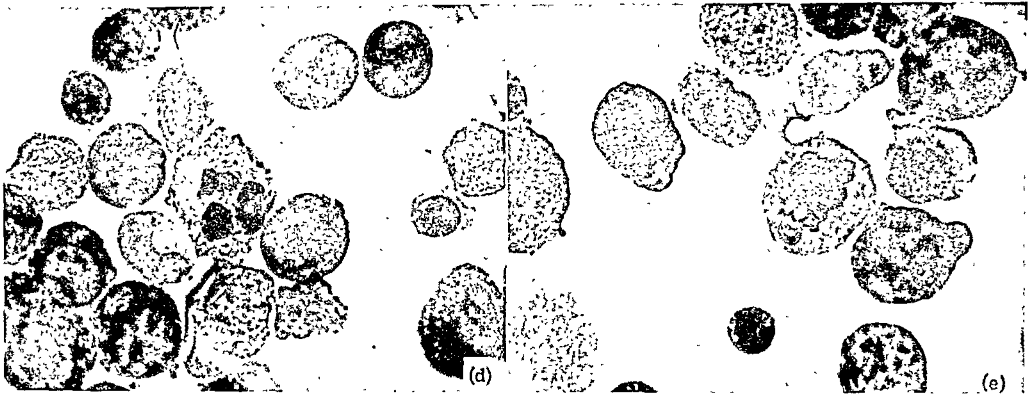


Fig. 8.—Photomicrographs of some pathologic aspects of the mitosis observed in the erythroid cells in acute erythemia. (×1,100; reduced ⅕.) *a*, Abnormal anaphase *b*, Metaphase (scattering chromosomes). *c*, (?) Tripolar division or division of lobated nucleus. *d*, Tripolar division. *e*, (?) Abnormal mitosis.

TABLE III.

DATE	TOTAL NUCLEATED CELLS/MM.^{3}	NUCLEATED RED CELLS TOTAL*	HB†	PE†	BN†	PN†	ON†	RETICULOCYTES (%)	RBC ($\times10^6$)	HEMOGLOBIN (GM.)
April 5	5,600	554 9.9%	–	50 9.0%	101 18.0%	356 64.0%	50 9.0%	10.0	3.29	6.8
April 16	2,750	–	–	–	–	–	–	13.0	4.11	8.2
April 23	4,750	137 2.9%	–	–	–	137 100%	–	1.2	3.65	10.3
May 2	6,600	125 1.9%	–	–	–	125 100%	–	2.6	4.00	8.9
May 6	12,350	1,111 9.4%	–	111 10.0%	555 50.0%	111 10.0%	333 30.0%	3.0	3.50	7.9

*Absolute number and percentage of total nucleated cells.

†HB, hemocytoblast. PE, proerythroblast. BN, basophilic normoblast. PN, polychromatic normoblast. ON, orthochromatic normoblast.

nodes in the cervical, axillary, and inguinal regions. The liver was palpable 10 cm. below the right costal margin, the spleen 19 cm. below the left costal margin. The rest of the examination proved noncontributory.

A diagnosis of acute erythromyelosis was made on laboratory findings (see Hematologic Evaluation) (Table III).

The child was hospitalized. His clinical condition at first was fair and he spent most of the time up and about. There was no change in the size of the spleen, liver, or lymph nodes. After one month in the hospital he developed fever and further distention of the abdomen accompanied by pain, with no indication as to origin. Nose, throat, and blood cultures were negative. Death occurred during sleep, five days after this episode started, and three months after the onset of first symptoms.

HEMATOLOGIC EVALUATION (CASE 2)

Peripheral Blood (Table III).—The erythroid series showed hypochromic anemia (mean corpuscular hemoglobin 20.6 $\gamma\gamma$) with anisopoikilocytosis, slight to moderate spherocytosis, with the presence of schizocytes and polychromasia. Following admission, the hemoglobin values were kept at a level between 9 and 11 Gm. by blood transfusions. A significant decrease in the number of reticulocytes was noted after the first transfusion. Since then they had remained within normal limits. Nucleated red cells were present throughout the course of the disease, their number ranging between 1 and 9 per cent of the total nucleated cell count. All elements were represented from the hemocytoblast with erythroid characteristics (cells described in Case 1) to the orthochromatic normoblast, the percentage of the more immature cells being increased in the terminal phase of the disease.

In the myeloid series, the corrected number of white cells remained within normal range (2,750 to 11,239 per cubic millimeter). A marked shift to the left was noted with no particular morphological alterations. The lymphocytes were low in number. The monocytes showed no significant change. Platelets were constantly low (3,000 to 38,000 per cubic millimeter).

A spontaneous diminution of all the nucleated cells from the initial value

CASE 2

	WHITE CELLS							
TOTAL*	MYELOBLASTS	PROMYELOBLASTS	MYELOCYTES	METAMYELOCYTES	POLYMORPHONUCLEAR LEUKOCYTES	LYMPHOCYTES	MONOCYTES	PLATELETS
5,046 90.1%	150 3.0%	50 1.0%	400 8.0%	550 11.0%	2,750 55.0%	700 14.0%	400 8.0%	19,000
2,750 100%	–	–	–	–	1,250 45.0%	1,000 37.0%	500 18.0%	26,000
4,613 97.1%	350 8.0%	150 2.0%	150 2.0%	260 8.0%	2,453 56.0%	600 13.0%	650 9.0%	38,000
6,475 98.1%	259 4.0%	324 5.0%	324 5.0%	583 9.0%	3,561 55.0%	972 15.0%	452 7.0%	3,000
11,239 90.6%	450 4.0%	225 2.0%	674 6.0%	337 3.0%	7,305 65.0%	1,348 12.0%	900 8.0%	–

was noted, subsequently followed by a general rise.

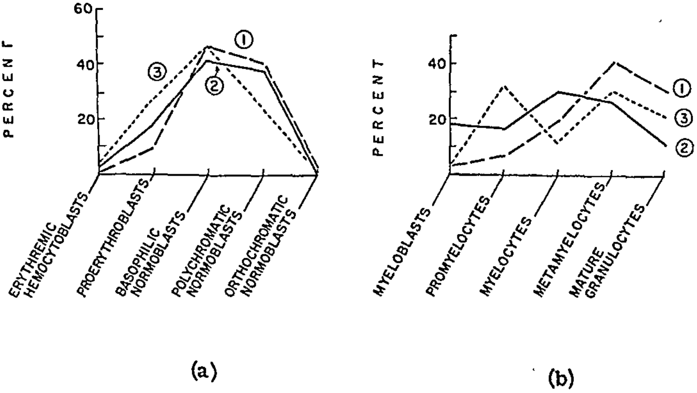
Bone Marrow.—

Bone marrow samples were obtained as previously described in the data on Case 1, and maturation curves were done on the smears from the marrow aspirate. All the samples were markedly hypercellular, showing conspicuous erythroid hyperplasia.

Erythroid:myeloid ratios:

April 3	1:1
April 16	2:1
April 25	2:1

The erythroid elements, their type and percentage, are illustrated by the maturation curves (Fig. 9, *a*) which show a maturation arrest at the level of the basophilic normoblast in all samples and a marked increase of the



(a) (b)

Fig. 9.—Case 2. *a*, Maturation curves of the erythroid series in the bone marrow. *b*, Maturation curves of the myeloid series.
1, April 3. *2*, April 16. *3*, April 25.

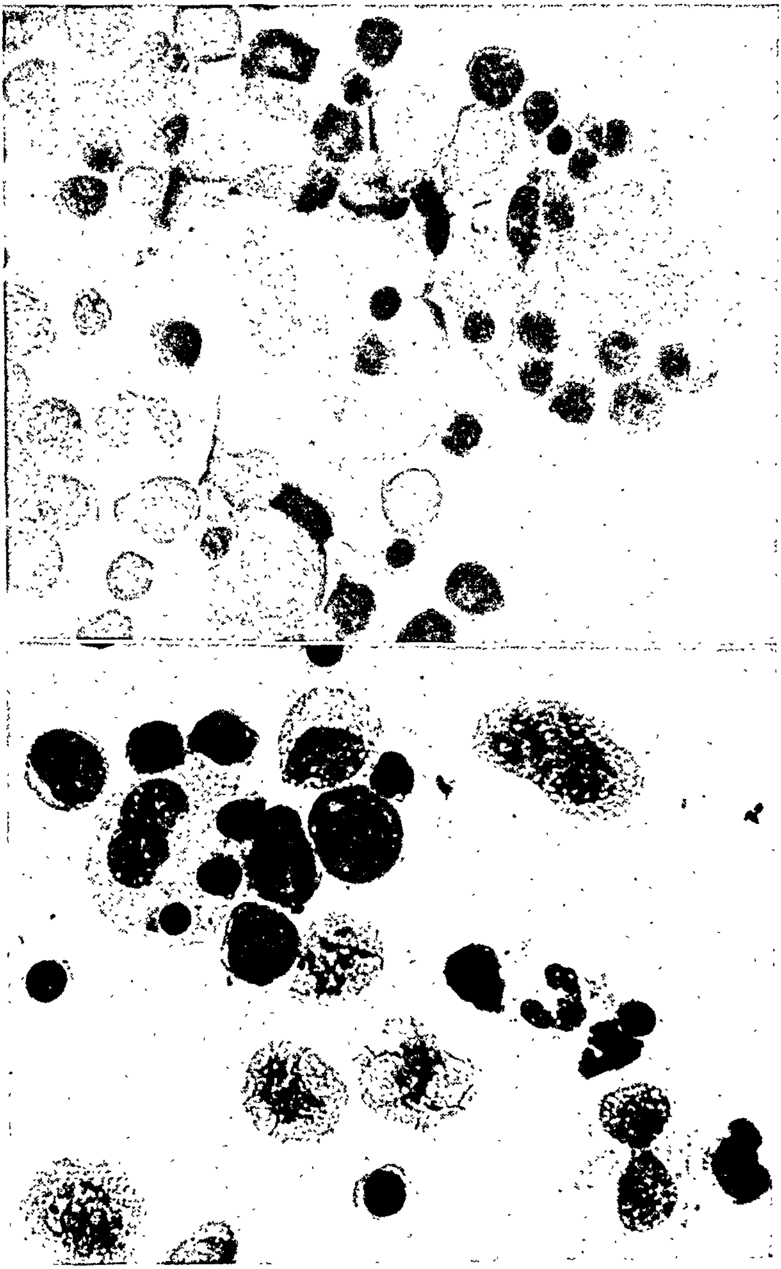


Fig. 10.—Photomicrographs of the bone marrow aspirate showing macrophages trapping numerous basophilic, polychromatic, and orthochromatic normoblasts. (×850.)

proerythroblasts and absence of orthochromatic normoblasts. In all three samples, about 20 per cent of all nucleated cells were represented by immature cells as the already described paraerythroblast. The pathological changes of the erythroid cells were identical with those in Case 1. An additional feature, however, was present in this patient's bone marrow—the presence of numerous macrophages, many of them containing nucleated red cells in all stages of maturation (Fig. 10). Mitotic figures were seen in an average of 4 in 100 cells, some of them suggesting abnormality (Fig. 8).

In the myeloid series (Fig. 9, *b*), the first curve shows a completely normal maturation. The second curve shows a shift to the left. The last obtained bone marrow specimen shows a diphasic type of curve, the result of an increase in promyelocytes and a decrease in myelocytes. No particular morphological changes were observed.

The megakaryocytes were extremely rare in all the bone marrow samples obtained.

Tests.—

The blood group was O, Rh positive.

The Coombs test, direct and indirect, was repeatedly negative.

Total serum bilirubin (April 7) 0.63 mg. per cent; free 0.25 mg. per cent.

Red-cell fragility was normal.

The tourniquet test was 3 plus, clotting time 2 minutes.

Repeated skeletal surveys and chest x-rays were negative.

Evaluation of the clinical and hematological findings points to a diagnosis of acute erythromyelosis evolving toward erythroleukemia. This diagnosis was confirmed at autopsy.

Pathological Diagnoses.—

Acute erythromyelosis, with infiltration of spleen, stomach, small intestine, appendix, colon, pancreas, liver, kidneys (Figs. 11, 12), bone marrow by cells of the same type as were seen in the bone marrow samples during life.

Lymphadenopathy, cervical, inguinal, axillary, portal, mesenteric, peripancreatic, periaortic, hilar, mediastinal.

Hemorrhage, petechial and ecchymotic, of skin, conjunctivae, kidneys, liver, lungs.

Leukocytosis due to immature erythroid cells.

Osteoporosis, moderate.

Edema of feet, thighs, perineum, mesentery, lungs.

Pleural effusion, bilateral (left 175 c.c., right 100 c.c.).

Atelectasis, bilateral, partial.

Fatty metamorphosis, liver.

Colloid depletion, thyroid.

Atrophy, thymus.

Hypotrophy, adrenals, with multiple cortical adenomas.

Scars, left cervical, and left knee.

Bacteriology:

Heart:	No growth
Lungs:	No growth
Pleural cavity:	No growth

CASE 3

D. B. was a white girl, aged 3 years and 2 months. The paternal grandmother had pharyngeal cancer. A cousin has diabetes. There were no siblings. Birth and development were normal. There were regular immunizations and the child remained in good health to the present illness.

At the end of July, 1956, the girl became anorexic and appeared tired. Soon thereafter she presented ecchymoses of the skin after very slight trauma. Weakness gradually increased

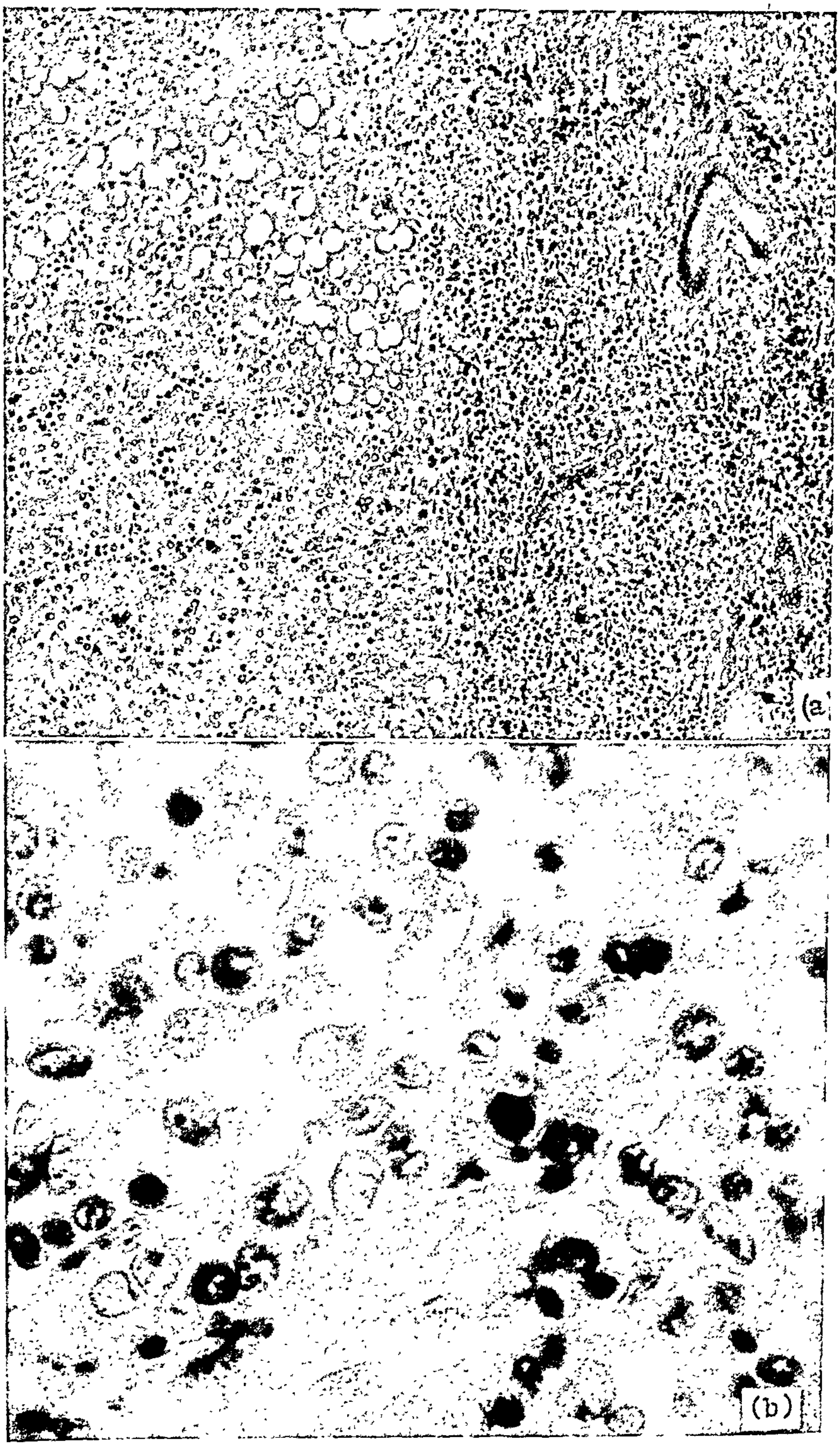


Fig. 11.—Photomicrographs of liver showing the heavy infiltration with immature erythroid elements and fatty metamorphosis. (*a*, ×200; reduced ⅛. *b*, ×1,250; reduced ⅛.)

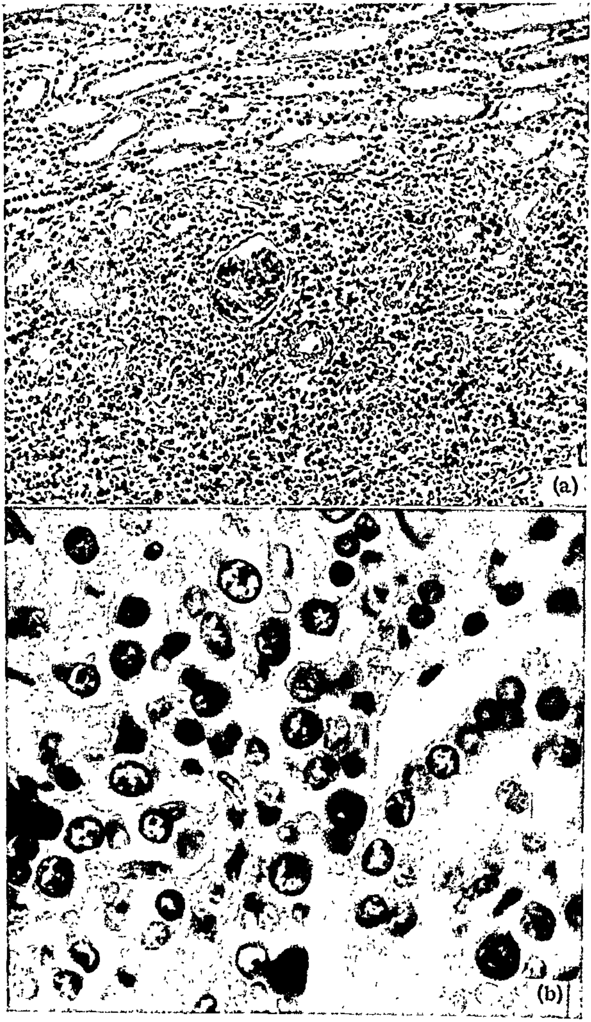


Fig. 12.—Photomicrographs of the kidney showing the heavy infiltration of the cortex by the immature erythroid cells. (*a*, ×200; reduced ⅛. *b*, ×1,250; reduced ⅛.)

TABLE IV. CASE 3

DATE	TOTAL NUCLEATED CELLS/MM.^{3}	"BLASTS"*	NUCLEATED RED CELLS/MM.^{3}	WHITE CELLS							
			TOTAL*	TOTAL*	MYELOBLASTS	PROMYELOCYTES	MYELOCYTES	METAMYELOCYTES	MATURE GRANULOCYTES	LYMPHOCYTES	MONOCYTES
Sept. 21	24,000	10,250 42.7%	8,250 34.2%	5,500 22.9%	789 14.3%	945 17.2%	1,100 20.0%	160 2.9%	2,020 36.7%	472 8.6%	14 0.3%
Sept. 27	25,000	13,340 53.4%	7,000 28.0%	4,660 18.6%	180 3.9%	180 3.9%	900 19.3%	180 3.9%	2,160 46.4%	1,060 22.7%	–
Oct. 3	72,000	38,700 53.8%	23,000 32.0%	10,300 14.2%	–	–	4,900 47.6%	–	5,400 52.4%	–	–
Oct. 11	72,000	48,400 67.2%	17,000 23.6%	6,600 9.2%	–	–	2,200 33.3%	500 7.6%	3,350 50.8%	550 8.3%	–
Oct. 18	15,900	7,490 47.1%	5,220 32.8%	3,190 20.1%	–	–	210 6.6%	300 9.4%	1,190 37.3%	1,280 40.1%	210 6.6%
Oct. 25	20,200	11,530 57.1%	5,250 26.0%	3,420 16.9%	–	300 8.8%	745 21.8%	–	1,045 30.6%	730 21.3%	600 17.6%
Oct. 28	37,000	17,200 46.5%	11,650 31.5%	8,150 22.0%	–	500 6.1%	750 9.2%	200 2.4%	2,000 24.5%	3,700 45.4%	1,000 12.2%
Nov. 8	89,000	52.700 59.2%	18,900 21.2%	17,400 19.6%	–	2,100 12.1%	2,800 16.1%	1,000 5.8%	6,700 38.6%	2,700 15.6%	2,100 12.1%
Nov. 15	40,000	22,050 55.1%	7,500 18.7%	10,450 26.1%	–	325 3.1%	975 9.3%	880 8.4%	4,050 38.8%	4,220 40.4%	–
Nov. 21	24,400	14,685 60.2%	4,570 18.7%	5,145 21.1%	–	198 3.8%	390 7.6%	170 3.4%	3,000 58.3%	1,190 23.1%	197 3.8%
Nov. 27	19,100	15,870 83.1%	1,350 7.0%	1,880 9.9%	–	178 9.5%	178 9.5%	106 5.6%	1,240 65.9%	178 9.5%	–
Dec. 4	15,100	11,690 77.4%	1,180 7.8%	2,230 14.8%	–	140 6.3%	570 25.6%	100 4.5%	600 27.0%	700 31.5%	120 5.4%
Dec. 17	18,100	14,360 79.3%	1,340 7.4%	2,400 13.3%	–	–	302 12.6%	50 2.0%	302 12.6%	1,676 69.8%	70 2.9%
Dec. 24	44,800	30,620 68.4%	4,600 10.3%	9,580 21.3%	–	810 8.5%	2,820 29.4%	410 4.3%	2,020 21.1%	2,420 25.3%	1,100 11.5%
Dec. 31	43,000	18,560 43.2%	5,950 13.8%	18,490 43.0%	1,480 8.0%	2,960 16.0%	7,050 38.1%	1,520 8.2%	3,300 17.8%	740 4.0%	1,440 7.8%

*Absolute number and percentage of total nucleated cells.

and in mid-September she had a severe epistaxis and was admitted to the Tumor Therapy Clinic of The Children's Cancer Research Foundation.

Physical examination showed a well-developed white girl who weighed 15 kilograms. She was pale, and there were multiple ecchymoses. The liver was palpable 4 cm. below the right costal margin, the spleen 6 cm. below the left costal margin. There was generalized shotty lymphadenopathy. The rest of the examination was noncontributory. The blood group was O, Rh negative. A diagnosis of acute erythroleukemia was made from the laboratory findings (see Hematologic Evaluation).

The child was started on folic acid antagonist and, because of a general clinical improvement, was discharged from the hospital one week after admission. Shortly after, because of severe epistaxic, fever, and hematemesis, she was readmitted to the hospital, following which her condition slowly deteriorated, with no significant change in the hematological status.

Severe hemorrhagic manifestations and infections dominated the clineal picture. Seven weeks before she died, she developed a *Staphylococcus aureus* septicemia. During the last three weeks she was semiconscious, refused to take anything by mouth, had a high spiking fever (40 to 41° C.), melena, hematemesis, hematuria, and was covered with petechiae and ecchymoses. She also presented a generalized moniliasis. The spleen and liver were enlarged to the iliac crests.

The child died quietly on Jan. 6, 1957, three and one half months after her first admission, and five and one half months after onset of symptoms.

HEMATOLOGIC EVALUATION (CASE 3)

Peripheral Blood (Table IV).—

Normochromic anemia (mean corpuscular hemoglobin 28.5γγ was present with a moderate anisopoikilocytosis, occasional spherocytes and schizocytes, and polychromia. The reticulocyte count remained within normal range. The hemoglobin varied between 4.6 and 11.2 Gm. during the course of the disease and was maintained by numerous blood transfusions.

The peripheral blood was characterized by the presence of: (a) nucleated red cells; (b) "blast" cells, resembling DiGuglielmo's "microerythroblasts"[4]; (c) immature myeloid cells (Fig. 13).

The nucleated red cells, presenting the same pathological findings as described in Case 1, were present all through the course, ranging in value from 7 per cent to 34.2 per cent of the total nucleated cells. Cells in all stages of maturation were represented; prevalence of the immature elements over the mature was constant and, occasionally, the hiatus erythremicus was observed (Fig. 14). The "microerythroblasts" were small, round, with an extremely thin rim of cytoplasm deeply basophilic, and a reticular dark nucleus occasionally presenting one to three colorless nucleoli. The number of these cells dominated the picture (Table IV) and their absolute number varied markedly. In the myeloid series the myelocytes were constantly present during the course of the disease, the promyelocytes occasionally, while the myeloblasts were found only at the first and last stages. No unusual morphological changes were noted.

Bone Marrow.—

Two samples were obtained and studied as previously described. Both samples were hypercellular and showed marked erythroid hyperplasia.

Erythroid: myeloid ratio was as follows:

September 19	1:2
October 23	3:1

The erythroid elements, their type and percentage, are illustrated by the maturation curves (Fig. 15, *a*). In both samples there was an arrest of maturation at the level of the basophilic normoblast. The orthochromatic normoblasts were practically absent. In addition, the same pathological changes noted in Cases 1 and 2 were apparent. Numerous "paraerythroblasts" and "microerythroblasts" were present and some form of passage from these cells to the normal erythroid series was noted. Mitosis averaged around 1 in 100 cells.

The myeloid series (Fig. 15, *b*) showed marked increase of myeloblasts and promyelocytes and a marked decrease of the metamyelocytes and mature granulocytes. Myelocytes were practically absent. Megakaryocytes were extremely rare.

The clinical and hematological findings in this case point toward a diagnosis of acute erythroleukemia. The diagnosis was verified at autopsy.

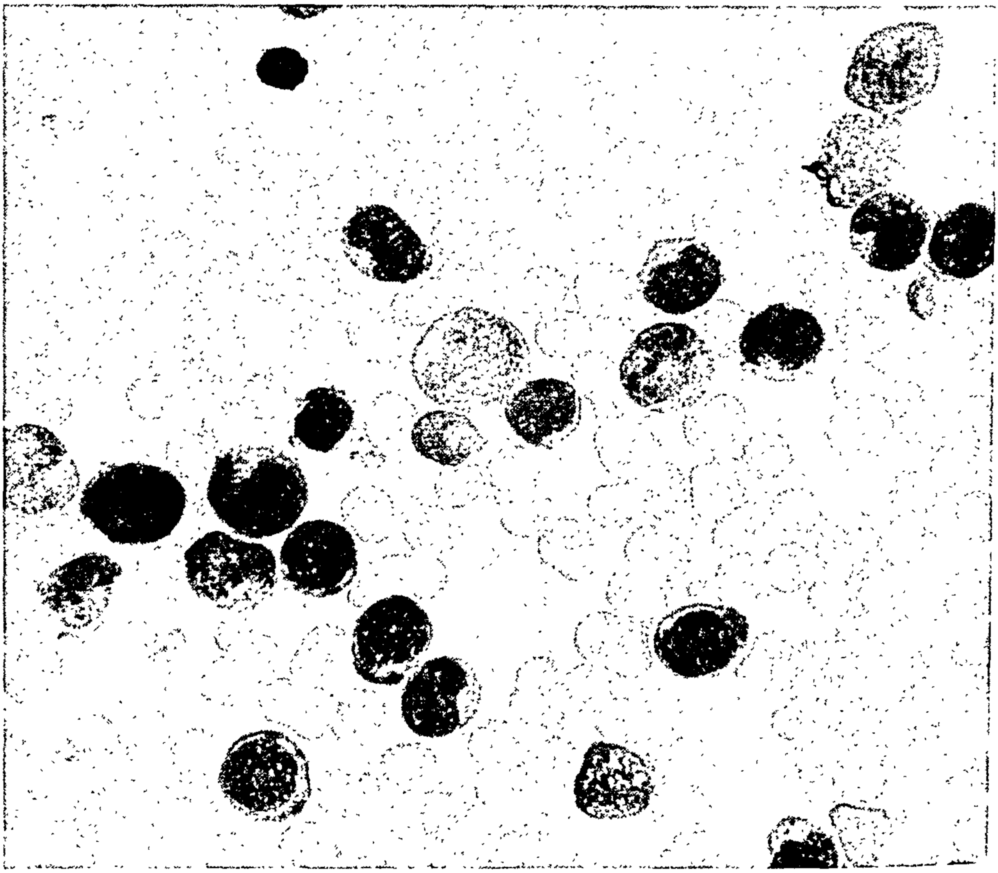


Fig. 13.—Case 3. Photomicrograph of the peripheral blood showing the presence of immature erythroid and myeloid elements. (×850.)

Pathological Diagnoses.—

Leukemic infiltration of bone marrow, spleen, lymph nodes, kidneys, adrenals, urinary bladder, uterus, vagina, and Fallopian tubes, with the same type of cells as were seen in the bone marrow during life.

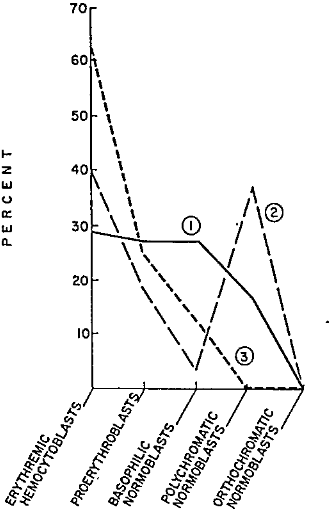


Fig. 14.—Case 3. Samples of the percentual distribution of nucleated red cells in the peripheral blood during the course of the disease.
1, September 21. *2*, November 8. *3*, December 17.

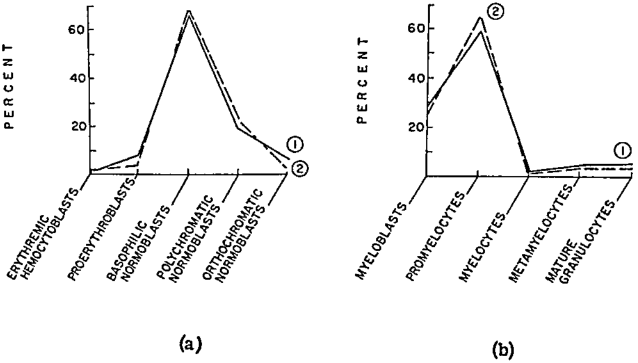


Fig. 15—Case 3. *a*, Maturation curves of the erythroid elements in the bone marrow. *b*, Maturation curves of the myeloid elements.
1, September 19. *2*, October 23.

Splenomegaly (115 grams compared with the normal 39).

Lymphadenopathy.

Thrombocytopenia with hemorrhages of heart, lungs, gastrointestinal tract, kidneys, urinary bladder, skin, lips, and gums.

Anemia with fibrosis of the heart.

Therapeutic effect (ACTH, mercaptopurine, transfusions): hyperplasia of the adrenals (with cytomegaly of the stratum fasciculatum); toxic gastritis; fibrosis of the spleen, slight; fibrosis of the bone marrow, slight, with focal necrosis of the costal metaphysis; hemosiderosis of spleen, liver, and lymph nodes.

Multiple bacterial and mycotic lesions: ulceration of the esophagus (? streptococcus); ulceration of the intestine (*B. coli*); ulceration of the vulva (agent undetermined); bronchopulmonary aspergillosis; moniliasis of liver and heart.

Fatty changes of the liver.

Meckel's diverticulum.

Bacteriology:

Heart:	No growth
Lungs:	No growth
Bowel:	*E. coli* *Alpha hemolytic streptococcus*

DISCUSSION

Various pathological changes in the erythroid series were encountered in a group of 754 children with miscellaneous types of acute leukemia. The particular combination, however, of the several pathological changes compatible with DiGuglielmo's disease was found to be extremely rare in this age group. Only two cases of acute erythromyelosis and one of erythroleukemia in children were diagnosed.

Hematologically and clinically, these cases were well characterized by hyperplasia, anaplasia, dysplasia, and metaplasia of the erythroid system, as well as by severe anemia, erythroblastosis (with steady increase in the circulation of progressively less mature erythroblasts), thrombocytopenia with hemorrhagic manifestations, hepatosplenomegaly, ulceronecrotic lesions of the oral cavity, intermittent fever, and, finally, the short and fatal course. The hematological and clinical manifestations of these diseases have been reported several times and extensively discussed. For this reason we shall limit our discussion to findings of particular interest presented by our three patients.

The severe, progressive anemia is particularly characteristic of these diseases. Numerous mechanisms have been implicated in its pathogenesis:

A. Decreased production of mature erythrocytes. Although the bone marrow is overcrowded with erythroid elements, the maturation of the red cells is usually arrested at a prehemoglobinized stage, as is well demonstrated by the reported maturation curves (Figs. 6, 9, 15), although, in the first stages of the disease, a certain percentage of erythroid cells still retain their ability to mature (hiatus erythremicus). In the natural progress of the disease, the reproduction of these cells stops, as is illustrated (Figs. 1 and 2) by the decrease and then the disappearance of the reticulocytes, the ortho- and polychromatic elements from the blood and the bone marrow.

B. The shorter life span of the erythrocytes. This, very likely, is due to intrinsic defects and/or abnormal formation indicated by the poor and irregular hemoglobinization and morphological changes.

C. Increased destruction. The hyperplasia of the reticuloendothelial system, increased erythrophagocytosis, and splenomegaly are constant findings in these diseases.

Usually, phagocytosis is directed against aged or damaged red cells, but in one of our patients (Case 2) the phagocytic activity was directed against all the erythroid elements. The bone marrow examinations revealed numerous macrophages which contained not only erythrocytes but all types of erythroid cells from the proerythroblast to the orthochromatic normoblast (Fig. 10). Together with the increased activity of the reticuloendothelial system, the cytological abnormalities and metabolic or immunological changes of the erythroid cell might be considered in an attempt to explain this finding.

In acute erythremic myelosis the presence of cells referred to as "megaloblastiform" has been reported.[3, 30] Similar cells were observed in one of our patients J. P. (Case 1). In this case, together with the presence of these megaloblastic cells, some macrosomia of the metamyelocytes in the bone marrow and a marked hypersegmentation of the nuclei of the mature granulocytes were observed. An interesting observation was the disappearance of these "megaloblastic" cells and the normalized maturation of the leukocytes in coincidence with the administration of high amounts of vitamin B_{12}. No changes, however, were noted in the progression of the anemia and the other pathological alterations of the erythroid cells. Thus, these megaloblastic changes might be interpreted as being due to a secondary deficiency of folic acid or vitamin B_{12} deriving from enormously increased cell reproduction. This interpretation coincides with the one given to explain the megaloblastic changes sometimes observed in the acute leukemias.[31]

Numerous findings indicate pathogenetic similarity between acute erythromyelosis, erythroleukemia, and malignant processes.[25, 32, 33] All three of our patients presented similar bone marrow changes and the maturation curves of the erythroid series showed a constant arrest of maturation. The persistent shift to the left as the disease progresses indicates that this inability to mature becomes more and more marked. Thus, the already increased production of immature elements encounters this block which moves steadily backward, resulting in an increase in the progressively less differentiated population of cells. This behavior will explain the various phases occurring during the evolution of this disease and may also be compared with that of some types of anaplastic malignancies where progressively undifferentiated cells may be observed.

Our three patients also showed extramedullary erythropoiesis. It may be seen that this finding of erythroid ectopic growth also appears to parallel the metastatic behavior of most malignancies, and should not be interpreted solely as a compensatory effort to control the anemia, since it was not limited to potential hematopoietic organs but was found, as well, in other organs such as the intestine, kidneys, pancreas, etc.

The progressive increase of the "erythroblasts" in the peripheral blood and their increasing immaturity are typical findings of the disease. The temporary spontaneous decrease

Splenomegaly (115 grams compared with the normal 39).

Lymphadenopathy.

Thrombocytopenia with hemorrhages of heart, lungs, gastrointestinal tract, kidneys, urinary bladder, skin, lips, and gums.

Anemia with fibrosis of the heart.

Therapeutic effect (ACTH, mercaptopurine, transfusions): hyperplasia of the adrenals (with cytomegaly of the stratum fasciculatum); toxic gastritis; fibrosis of the spleen, slight; fibrosis of the bone marrow, slight, with focal necrosis of the costal metaphysis; hemosiderosis of spleen, liver, and lymph nodes.

Multiple bacterial and mycotic lesions: ulceration of the esophagus (? streptococcus); ulceration of the intestine (*B. coli*); ulceration of the vulva (agent undetermined); bronchopulmonary aspergillosis; moniliasis of liver and heart.

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B. The shorter life span of the erythrocytes. This, very likely, is due to intrinsic defects and/or abnormal formation indicated by the poor and irregular hemoglobinization and morphological changes.

factor did not affect the disease. Vitamin B_{12}, on the other hand, corrected the megaloblastic changes and the granulation defects of the neutrophils, but it did not appear to be of benefit in the management of the disease.

2. It is a well-established fact that, in childhood especially, corticosteroids and ACTH frequently will induce remission of acute leukemia. These agents have, in addition, the ability to control the hemolytic processes and the hemorrhagic manifestations which very often accompany the leukemic processes. Two of our patients (Nos. 1 and 3) were given prednisone in high doses (30 to 40 mg. per day) throughout the course of their disease, or ACTH (25 units per day, intravenously). The impression was that the hemolysis was diminished, at least to a limited extent, and that the hemorrhagic manifestation in one of the two cases was temporarily controlled. These drugs were also found to be of some use for their antiasthenia effect. They did not, however, induce remissions or affect the main pattern of the disease.

3. The folic acid antagonist, Methotrexate, and purine antagonist, 6-mercaptopurine, were used in Case 1 and Case 3. In the latter, some changes were noted in the absolute number of cells in coincidence with the administration of these drugs, but, as already stated, the evaluation is extremely difficult. They failed, however, to induce temporary remission.

4. An alkylating agent, chlorambucil, was used in Case 1. The concept guiding our choice was the knowledge of its activity against cells of the reticuloendothelial system. The involvement of this system in the disease and the cytological characteristics of most of the immature erythroid elements resembling histioid cells suggested the use of this drug. No effect was produced on the progress of the disease. A possible fleeting effect upon the number of circulating "blasts" was noted after a high dose (0.420 mg. per kilogram per day) of chlorambucil was administered (Fig. 5).

SUMMARY

Clinical histories of two children with acute erythromyelosis and one child with acute erythroleukemia are reported and the difficulty of differential diagnosis considered.

The hematological and clincal findings are evaluated and followed throughout the patient's course.

The pathogenic mechanisms of the anemia are discussed.

A specific phagocytosis against nucleated red cells is documented.

The anaplastic and dysplastic changes of the erythroid system, the invasion of multiple organs, and the logarithmic progression of pathological cells in the blood stream (observed in Case 1) suggest strong similarity between erythromyelosis and the neoplastic diseases.

Various lines of therapeutic approach are described.

Grateful acknowledgment is made to Dr. John M. Craig for the "Pathological Diagnoses" utilized in this report, and to the nurses and Clinical Staff who assisted in the collection and organization of the material.

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X-IRRADIATION EFFECTS ON THE HUMAN FETUS*

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RADIATION insult is immediate, but the biological manifestations may be long delayed. Therapeutic irradiation of the pregnant woman can cause microcephaly and other anomalies as well as long-term subtle sequelae in the child. We now have some information relative to the stage in development and the exposure level which will cause demonstrable anomalies. We do not know the lowest level of exposure which will produce the more subtle effects.

Our evidence comes from controlled experiments with mammals other than man, and from some incidental and accidental human fetal exposures. When one plots the sequence of organogenesis in the mouse or rat with that of the human embryo, using the two time scales, it is obvious that the development of these mammalian forms is basically similar.[9] (Table I and Fig. 1.)

Every irradiation-produced anomaly in the human fetus has been experimentally produced in the mouse or rat embryo following irradiation at a comparable stage of development.[7] It is justifiable, therefore, to extrapolate from the mouse or rat to the human in regard to the specific organ susceptibility periods with the proviso that any statement is prefaced with the word "probable." However, since there is a time differential factor of

Table I. Correlations in Development: Mouse and Man

AGE IN DAYS: EMBRYO			
MOUSE	MAN	MM. LENGTH	DEVELOPMENTAL STAGE IN HUMAN: ORGAN PRIMORDIA
5	11		Implantation
8	20.5	(1.5)	Primitive streak, blood islands, neural groove
9	25.5	(2.4)	Primordia of sense organs, thyroid, limbs, muscles, pronephos, branchial arches. Extra embryonic vasularization
10.5	28.5	(4.2)	Gastrointestinal tract + derivatives, meso-metanephros, 31 somites, yolk hemopoiesis. Abundant neuroblasts
11.5	33.5	(7.0)	Genital ridge, spleen + bronchial buds, cardiac septa, 38 somites
12.5	36.5	(9.0)	Bilobed thyroid, nerves + ganglia differentiating
13.5	38.0	(12.0)	Sexless gonad primordia, liver hemopoiesis, brain flexures, limbs, thymus, gastrointestinal tract actively differentiating
14.5	47.0	(17.0)	Cerebral hemispheres, corpora striatum, thalamus, spleen, blood vessels all actively differentiating
15.5	65.0	(40.0)	Cerebral cortex, intestinal, villi, thyroid follicles, first [illegible]
16.5	[illegible]	[illegible]	[illegible] roglia in [illegible]

Note: I[illegible] tus from about day [illegible]

From the Radiological Research Laboratory, Columbia University.

*Based upon Panel Discussion, American College of Surgeons, Atlantic City, Oct. 14, 1957.

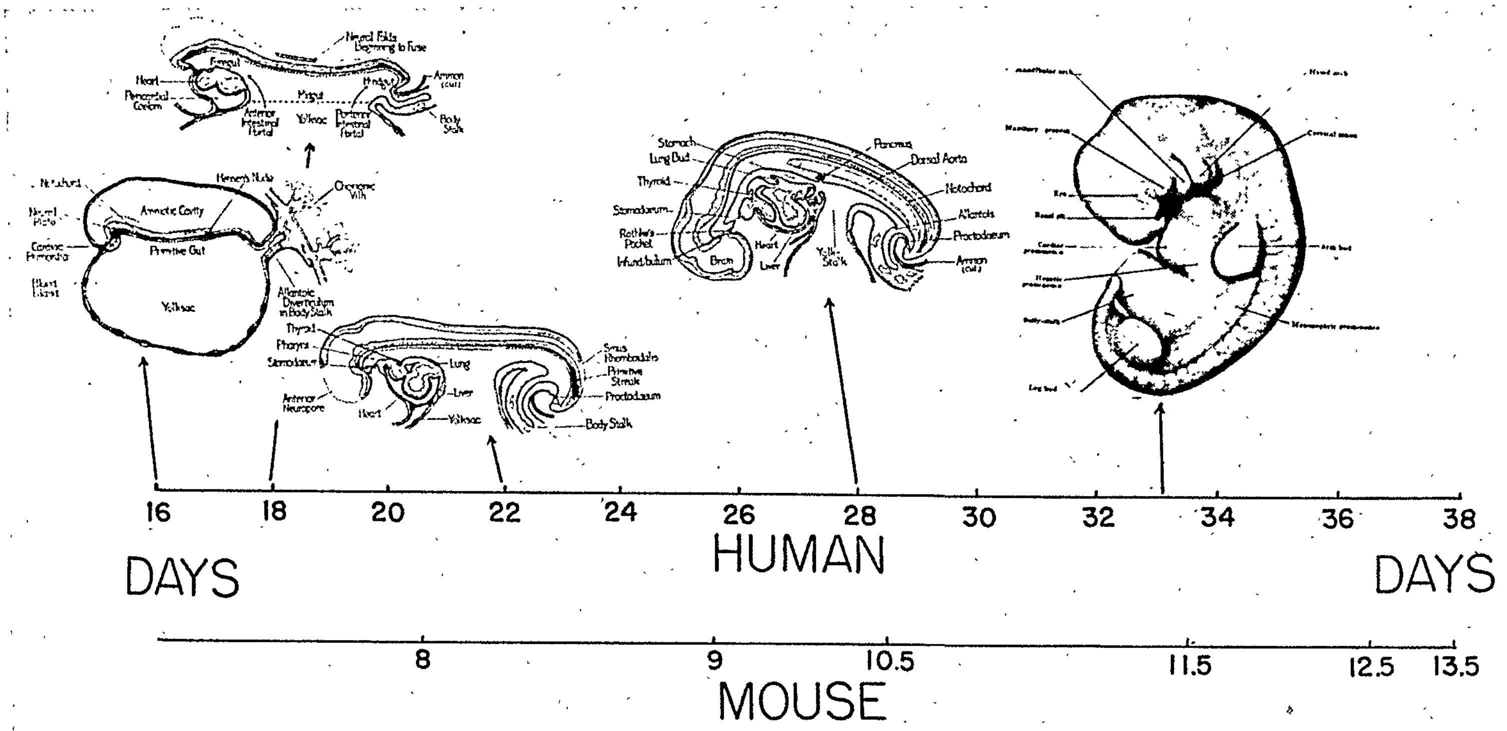

Fig. 1.—Most irradiation-critical stages in human and mouse development. (Drawings of the development of the human embryo are taken from Patten, B. M.: Human Embryology, 1953, ed. 2, Courtesy of Blakiston Div., McGraw-Hill Book Co., by permission of the author.)

about 13, the period of greatest sensitivity in the human is likewise extended. Thus far we have found no exceptions in the extrapolations. Further, in experimental studies on the mouse[20] it seems evident that effects on the embryo or fetus are direct and not mediated through the mother. There is some evidence that pregnancy actually gives the mother better survival value,[13] at least until delivery. posure of as little as 40 r to the embryo on about day 28 might conceivably produce serious abnormalities. Irradiation of the rat embryo at a comparable stage has caused anencephaly or total absence of brain.[6] Such monstrosities can come to term, but cannot survive. It is during this period that all of the organ primordia are laid down by rapid differentiation from primitive cell types.

TABLE II. MAJOR ABNORMALITIES FOUND IN THE MAMMAL (HUMAN, RAT, MOUSE) FOLLOWING FETAL X-IRRADIATION

BRAIN	EYES	SKELETON	MISCELLANEOUS
Anencephaly	Complete absence	Uniform reduction: stunting	Situs inversus
Porencephaly	Microphthalmia	Reduced skull dimensions	Hydronephrosis
Microcephaly	Microcornea	Vaulted cranium	Hydroureter
Encephalocele	Coloboma	Narrow head	Absence of kidney
Reduced medulla	Narrow iris	Cranial blisters	Degenerate gonad
Cerebral atrophy	Absence of lens	Spina bifida	Atrophy of lower extremities
Mental retardation	Open eyelids	Reduced and deformed tail	Cutaneous depigmentation and hyperpigmentation
Idiocy	Strabismus	Overgrown and deformed feet	Motorial disturbances of extremities
Deformities:	Retinoblastoma	Digital reductions	Increased probability of leukemia
Narrow aqueduct	Hypermetropia	Abnormal limbs	
Hydrocephalus		Syndactyly	
Rosettes in cortex and medulla		Brachydactyly	
Dilation of third and lateral ventricles		Odontogenesis imperfecta	
Neuroblastoma		Exostosis on proximal tibia	
Herniated brain		Metaphysis	
		Amelogenesis	

Implantation of the human ovum takes place at about day 10 or 11 after insemination.[10] Radiation tolerance during this preimplantation period is not known. The most radiosensitive period in the entire prenatal life of the human probably occurs from about day 18 through about day 38, immediately following implantation. After day 38, higher levels of exposure are necessary to produce anomalies. This is because during this earlier period there is a great abundance of embryonic cells in their most radiosensitive stage. It is now believed that an ex-

We know that the adult neuron can tolerate an exposure of 10,000 r, the embryonic neurectoderm can tolerate only about 400 r, while the transforming neuroblast can tolerate no more than 40 r.[5] The most radiosensitive stage in the etiology of a cell is during the transformation from its embryonic to its adult stage, whether it be a neuroblast, myoblast, osteoblast, or erythroblast.[14, 15] During this embryonic period of about day 18-38 such transformations are occurring in almost every one of the tissue varieties of the human embryo. One might suspect that fractionation of exposure might reduce the incidence of malformations, but this is not so.[1] Actually the severity of embryonic defects is far greater in response to fractionation than to a single dose, probably because more organ primordia will be radiation-insulted during their respective critical stages of development. As has been pointed out,[22] this is also the period during which neither the woman nor her clinician might suspect a pregnancy. (Fig. 2.)

It can be assumed that high energy x-irradiations may be rather uniformly distributed throughout the embryo or fetus, which is a mosaic of actively differentiating cells and likewise a mosaic of varying sensitivities. Irradiation destruction is proportional to the number of radiosensitive cells, but the specific anomaly produced is related to the differentiating organ system(s) possessing such cells. During the period of most active differentiation one would expect to produce the maximum possible damage even with low level exposures. At later stages in development higher exposures are necessary to produce gross abnormalities. This in no way implies any linearity in fetal radiosensitivity. There are exposures below which *detectable* anomalies are rare. Effects are qualitative

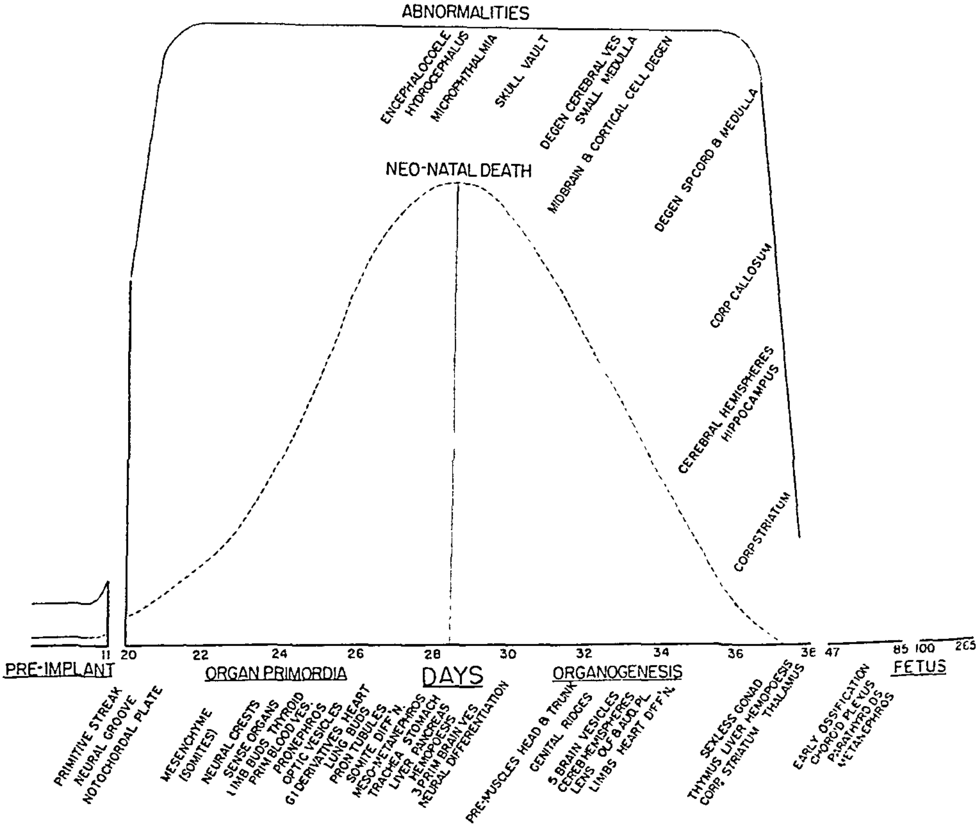

Fig. 2.—Time schedule of human organ primordia and irradiation-induced anomalies. This graph is a composite, based upon a similar graph for the mouse by L. B. Russell (1954) and such data as are available from normal human embryology (Patten, 1946) and from some human irradiation data. Microphthalmia, for instance, appears if the irradiation occurs while the optic vesicles are in active differentiation, about day 26.

rather than quantitative. However, one who is acquainted with the chronology of human development can predict rather accurately the types of anomalies to be expected following fetal exposure at any specified time, due simply to the presence of the dynamic and metamorphosing precursors of specific organs. After about day 40 the organ systems are largely established and gross teratologies can, but are less likely to, occur except at higher levels of exposure. However, the clinician should be cautioned in regard to possible fetal irradiation at any time for three basic reasons:

1. Wherever the primitive *germ cells* arise they will be highly sensitive to ionizing radiations. It is likely that they are at least as sensitive, if not more so, to radiation-induced mutations as are the adult germ or somatic cells. A mutation produced in such a single stem cell will multiply into all of its cellular progeny so that many functional gametes will be affected. The genetic effects of irradiation probably begin shortly after about day 32 when the genital ridges first appear, and continue through the reproductive life span of the individual. "The most precious asset of mankind today is the germ plasm which has enabled him to develop the culture we all enjoy. If current developments—of which increasing exposure to ionizing radiations is one—threaten the integrity of this germ plasm and are paving the way for the decline of our species, then here is a problem equal in magnitude to any with which we are currently confronted."[8]

2. The onset of teratological effects of x-irradiation is probably about day 18 in the human embryo, simultaneous with the development of the *neural groove,* the precursor of the *central nervous system.* During the next few weeks the neural axis and primary brain are organized. As the various organ systems develop they become invested with neural components, emanating from this growing central nervous system. These neuroblasts are among the most radiosensitive of all cells, and since they are found throughout the embryo and fetus, radiosensitivity is widespread. Irradiation of neuroblasts to 40 r, wherever they are found, usually results in their necrosis and death, with the consequent neural deletions. Such deletions will be the more obvious and widespread the earlier the developmental stage irradiated. There is undoubtedly functional damage at levels too low to be manifest by any histopathological test. Microcephaly, a common sequela of fetal irradiation, may not be apparent upon histological examination regardless of the degree of neural loss. The brain may be a miniature of the normal, uniformly deficient in neural elements. Some 64 per cent of the children exposed in utero to atomic bomb radiations within 1,200 meters, and who appeared normal at delivery, showed microcephaly with mental retardation by 4.5 years of age. There was no microcephaly among the 194 similar pregnancies beyond the 1,200 meters.[12] "Among 30 women who were pregnant at the time, who were within 2,000 meters of the hypocenter at Nagasaki, and who bore signs of radiation exposure, there resulted 7 fetal deaths (23%), 6 neonatal and infant deaths (26%) and 4 instances of mental retardation (25 %) among the 16 survivors (53%). The overall morbidity and mortality

was 60%.''[26] Mothers within the same 2,000 meters but without radiation exposure signs had over-all mortality of offspring of only 10 per cent, and, in distant controls, it was 6 per cent. It is believed that irradiation-damaged cells cannot recover, but since the fetus also possesses many early undifferentiated and less radiosensitive embryonic cells, it has remarkable powers of topographical regeneration and repair following phagocytosis of the irrevocably damaged cells. However, regeneration is never complete and the neural deletions which result are responsible for the microphthalmia, microcephalia, neural insufficiencies, and other nervous disorders which often follow fetal irradiation.

3. It is now known that prenatal irradiation increases the probability of *leukemia* in young children, even though a linear relation is yet unproved. ''The dose of irradiation received by the fetal gonads during diagnostic pelvimetry frequently exceeds 2.5 r. The present investigation suggests that, besides causing genetic damage, this apparently harmless examination may occasionally cause leukemia or *cancer* in the unborn child.''[24] A study of some 1,400 children showed that the probability of leukemic death was doubled in those who had had fetal irradiation. The latent period of this and other cancer developments may be years or decades, but until disproved it can be presumed that carcinogenesis is initiated more readily in the more radiosensitive embryonic cell, particularly when the entire fetus is exposed and thereby rendered physiologically more susceptible.

There have been references in the literature to instances of fetal x-radiation which were not followed by gross anomalies, or human embryos which survived large exposures, came to term, and appeared to be ''normal'' by all pediatric tests. Three things must be said about these cases: First, As the fetus advances in age it is better able to avoid gross teratologies following x-irradiation. However, radiation tolerance, in terms of a specific number of roentgens at various fetal ages, has no meaning because some anomalies can be produced by irradiation at almost any prenatal period. Specific teratologies undoubtedly have varying thresholds at specific developmental moments, but cannot be quantitated. Second, Irradiation-damaged cells are phagocytized, and the fetus can, through limited reorganization of the remaining undamaged cells, maintain rather normal topography. Third, With advanced fetal age, damage to the scattered neuroblasts cannot be as readily detected. However, there is histopathological evidence of such effects.[3, 4] In some cases, while there was no detectable evidence of damage at birth, following fetal irradiation, there has been subsequent evidence that the child exhibited abnormal psychological behavior. This supports the thesis that there may be functional damage at levels too low to have structural corollaries. There can be no controls for these data. The range of human ''normality'' is so great, so inclusive of a large variety of debilities, that even if a child's potential I.Q. is reduced from 140 to 70 by fetal irradiation, he would still be considered as ''normal.'' Without elaboration, reference is made to two recent cases reported in the literature where mental and other conditions were directly attributable to fetal irradiation.[2, 11] There are sequelae to fetal irradiation which are not evident for many years, even besides the genetic mutations which affect future generations, such as the shortening of life, the development of cancer and cataracts, sterility, the increased susceptibility to disease, and numerous subtle and less evident factors which affect survival.

In conclusion, the embryo, particularly between days 18 and 38, and the later fetus, represent the most radiosensitive stages in the life of human beings, due largely to the presence of actively differentiating cells involved in organogenesis. During certain periods of development, monstrosities in the offspring may be produced by low level therapeutic or even diagnostic exposures of the pregnant woman. Teratologies are less likely as the embryo becomes a fetus and are never formed by irradiation of the fully developed adult. Nevertheless, the damaging effects of ionizing radiations become more subtle with advancing fetal age and may well produce viable but psychologically ill-adjusted individuals, the like of whom are currently contributing to our overcrowded institutions. As Hicks[5] has written, "From the social viewpoint it is probable that the production of an individual with a subnormal brain may be a worse catastrophe than one with almost no brain."

We simply cannot evaluate the deleterious effects of diagnostic and therapeutic irradiation of the fetus.

The x-irradiation of the pregnant woman, particularly in the early trimester, should be discouraged under all conditions, short of saving the life of the mother. Further, it would be a wise practice to determine the time of the prior menses in all radiological examinations of women in order to avoid the possibility of exposure of an unrecognized pregnancy during the most radiosensitive period at about 2.5 to 6 weeks.

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A physician's first duty is to his patient; his second only, to himself.

All quackery reverses this principle as its fundamental axiom. Every practitioner who reverses it is a quack. A man who follows it may be ignorant, but his ignorance will sometimes be safer than a selfish man's knowledge.

From an ADDRESS BY OLIVER WENDELL HOLMES, M.D., delivered in 1858 to the Medical Graduates of Harvard University, the Boston Medical and Surgical Journal.

MANAGEMENT OF BRONCHIAL ASTHMA IN CHILDREN

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WHEN a child is brought to a physician the diagnosis is the first consideration. The term "asthma" has been somewhat confusing because it has been applied to any condition in which wheezing occurs. Chevalier Jackson[1] long ago said that "all is not asthma that wheezes," and his statement has been corroborated by many others, including ourselves.

We do not like the loose term "asthma." We prefer the words "bronchial asthma." To us, bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough. It is usually preceded or associated with seasonal or perennial rhinitis, and with partial obstruction of the lower air passages.

We believe that all patients with true bronchial asthma are allergic. It is true that we cannot always demonstrate the causative allergen or allergens, especially in patients in whom the asthma has begun after the age of 40. In children the discovery of the allergen is almost always a comparatively simple matter. In 1952, for example, we obtained positive skin tests in 362 of 366 asthmatic children.[2]

Time will not permit an adequate discussion regarding the allergy survey. Needless to say, a good history will often unearth the symptoms and may even elicit the causative factor, e.g., ragweed or cat hair or eggs. The history must concern itself not only with possible allergic factors, but also with illnesses from the time of birth, with emotional problems, and with details as to previous immunizations.

The physical examination must be thorough, from head to foot, with special attention to the lungs and heart, as well as the nasal passages. Fluoroscopic examination of the chest follows, and x-ray films of the chest if findings seem suspicious. We carry out a complete blood count in each case, also a Kahn test, nasal smear, urine and sedimentation rate.

SKIN TESTS IN CHILDREN

Skin tests in children are so important as to warrant some discussion.

a. *Indications.*—Skin tests are indicated in almost all allergic conditions, especially bronchial asthma, hay fever, perennial allergic rhinitis, atopic dermatitis (eczema), and gastrointestinal allergies. They are usually useless in urticaria and migraine.

b. *Timing.*—Tests can be done from birth but we usually see our patients after the age of 2. We have done tests in children as young as 9 months, but skin reactions in infants are usually milder than in older children. Tests may be negative in asthmatic infants and positive in these same children when the tests are repeated a few years later.

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c. *Location of Tests.*—In infants and young children we are forced to use the back or chest. In the older children we do the tests on the arms, as in adults.

d. *Number of Tests.*—Important allergens may be missed if tests are done incompletely. One should test with all possible inhalant materials and also with those foods which the child eats. Some physicians do about 20 to 30 skin tests and consider that they have carried out a proper allergy survey. In many children this small number of tests is insufficient and poor results are apt to occur.

e. *Scratch and Intradermal Tests.*—Tests in children (and in adults) should first be done by the scratch method. This technique is safe and easy to perform, and children rarely complain. In fact, many enjoy these tests, especially if they are done on the forearms so that they can be seen by the child. Positive reactions can be obtained in about 75 per cent of asthmatic children. About 60 scratch tests can be done in one sitting.

Intradermal tests *must* follow if the scratch method has not yielded sufficient information. In children we usually do 20 to 25 tests by this technique and all at one sitting. Most of these intradermal tests are made with important inhalant extracts, e.g., pollens, fungi, house dust, animal, and miscellaneous derivatives. Food extracts are also used if the history is suspicious. If not, we omit intradermal food tests because reactions with food extracts are not nearly as accurate as with inhalant materials.

The combination of scratch tests first, followed by intradermals where necessary, yields at least 95 per cent of positive skin tests in asthmatic children. Those who do only scratch tests can expect not more than 75 per cent results. Those who do only intradermal tests are also wrong because (a) they are apt to bring on systemic reactions which might even be fatal, (b) they do fewer tests and thereby are likely to miss positive skin tests, and (c) intradermal tests are more painful.

f. *Precautions.*—Our patients have strict orders to avoid, for at least 48 hours, certain drugs which lessen skin test reactions. These drugs belong to the sympathomimetic group, e.g., ephedrine, epinephrine, and certain nasal sprays or drops, or the antihistaminics or combinations which contain them.

g. *Laboratory Skin Tests.*—Tests done by commercial laboratories, with perhaps a few exceptions, are apt to be misleading because the results of skin tests must be correlated with the history of exposure and with clinical trials. Some laboratory reports are very poor, and they may wrongly accuse such materials as paper or aspirin. In addition, if the patient is dermographic the reports are apt to show positive reactions to almost all the materials. In patients with severe dermographia the allergist usually resorts to the passive transfer technique. If the scratch and intradermal tests are both negative, the allergist will often continue tests by dropping pollen or fungi into the conjunctival sac or the nasal passages. Commercial laboratories do not carry out these techniques.

From the practical point of view, physicians who refer allergic individuals to commercial laboratories are usually given a list of positive skin tests, with little or no recommendations as to therapy. The physician is apt to be bewildered, especially if the number of positive reactions is large. Unless he is well trained in the field of allergy, the physician is then tempted merely to treat symptoms as they occur; he may not give the child the hyposensitizing injections which lead to an increase in resistance to the allergenic materials.

If, however, the child is referred to one who is interested in allergy and equipped to do thorough testing, the referring physician can have his patient sent back to him, along with a detailed written report. Solutions for hyposensitization (if indicated) will accompany the child, along with instructions as regards dosages. Suggestions for avoidance of primary allergens and secondary factors will be outlined in the report. The child will be asked to return to the allergist at intervals. Such cooperation between the referring physician and the allergist usually leads to good results. We strongly recommend this procedure for the pediatrician who is too busy to carry out thorough allergy surveys.

Children rarely outgrow bronchial asthma. We cannot emphasize this too strongly. Infectious types of asthmatic bronchitis tend to disappear, but the allergic types usually culminate in true bronchial asthma. Delay in allergy surveys, including skin tests, is apt to be followed by chronic asthma with emphysema and deformed chest.

TREATMENT

Therapy must be discussed under three headings: Specific, Symptomatic, and Preventive.

I. *Specific Therapy.*—

The specific management of asthmatic children consists of avoidance of causative allergens, with or without hyposensitization. This combination undoubtedly gives much better results than can be obtained from any kind of nonspecific therapy, e.g., psychosomatic, antibiotic, vaccines or ordinary medications.

A. *Avoidance* must be as thorough as possible. All causative allergens must be removed or avoided, even if the favorite cat or dog is to be taken from the home. In all of our patients with all-year-round symptoms of bronchial asthma and/or rhinitis, we urge the following:

1. The home must be spick and span from the allergic point of view.
2. All pillows in the entire home are to be either rubber or Dacron. Other types, including feather, kapok, or cotton, are to be permanently removed. They are not to be stored in the attic or in some closet, to be brought out for guests. This order includes "show" pillows in the living room or den.
3. All mattresses in the home are to be made of rubber, or are to be encased in zippered plastic material.
4. Rug pads are to be rubber or are to be removed. We urge floor coverings which are easily cleaned, e.g., tile, stone, or linoleum. Furniture should be rubber-filled, if at all possible.
5. No household pets are allowed in the home. These include cats, dogs,

canaries, and parakeets. Stuffed bed toys, e.g., Teddy bears, are forbidden.

6. Dusting is to be done by vacuum cleaners with attachments or by wet mop. Whisk brooms only push dust from here to there.

7. Basements are to be kept as dry as possible. Wet or damp basements are usually moldy and molds are important allergens.

8. The home itself should be located in as clean a neighborhood as possible. If the neighborhood is close to railroad tracks or to industrial fumes or gases we usually advise a change of address.

9. Allergy to a food is frequently proved by the history and by several clinical trials. In such cases the skin tests are usually positive. If this allergy to a food has thus been verified, that food should be avoided. The child must avoid not only eggs, for example, but all foods which contain egg, e.g., mayonnaise and certain cakes and puddings. Avoidance of some foods for some months may by itself bring about a degree of hyposensitization. Other foods, e.g., fish and nuts, are so potent that the sensitive individuals usually must avoid them for the rest of their lives.

Cooking of foods lessens the danger of symptoms. Hard-boiled egg and powdered milk, for example, are less allergenic than the raw food. This fact permits some less-allergic individuals to indulge in the cooked variety of foods.

Botanical relationships must not be overlooked. Certain foods belong to groups, e.g., the legumes (pea-bean) family, or the gourds, e.g., pumpkin, squash, or cantaloupe. Cauliflower, broccoli, and Brussels sprouts are closely related. Patients who are definitely sensitive to one food of a group must avoid or look with suspicion on other members of the group.

Skin testing with food extracts is very reliable for a few potent foods, e.g., fish, eggs, nuts, celery, and cottonseed. In sensitive individuals allergy to these foods is usually easily demonstrated by the scratch technique. One *must* prove allergy to foods by withdrawal of the suspected food and then by cautious trial. It is wise to prove such tests at least three times. The intradermal food reactions are often misleading.

All this brings to mind the case of an 8-year-old boy whom we first saw about a year ago. He had a history of perennial asthma almost since birth, along with recent hay fever. He had been skin-tested by the intradermal method; many positive reactions had been found to foods and to inhalant materials. Hyposensitization with the inhalant extracts was correctly given but, in addition, all the positive-reacting foods were forbidden this child. He was not allowed milk, chocolate, and many other foods. As a result the child came to our office weighing less than 50 pounds and he was almost skin and bones. His spirits were low because he was not allowed to play with other children when he had asthma and he had asthma most of the time.

We carried out skin tests by the scratch tests, followed by about 20 intradermal tests with milk, chocolate, and inhalant materials. We found that skin tests for foods were practically negative. We personally made him drink large glasses of milk and eat large amounts of chocolate ice cream. We continued injections of house dust, pollens and fungi, to which he is clinically allergic; we advised continuation of precautions against house dust, household pets, etc.

The results have been excellent. This boy has gained more than 10 pounds this past year; he has very little asthma; his appetite is excellent; he plays with other boys and recently was very proud because he broke a finger while playing baseball.

This case is just one of many in which allergists and other physicians have harmed their patients by relying on skin tests without regard to the fact that clinical allergy to these foods was not proved. We may forget that children need much food to live and to grow.

B. *Hyposensitization* (densensitization) consists of injections of increasing amounts of extracts of important allergens which cannot be avoided, e.g., house and occupational dusts, pollens, fungi, feathers, or animal danders. Results are usually good, especially when combined with as thorough avoidance of allergens as humanly possible. Actually, failure is rare as good to excellent results can be obtained in almost all asthmatic children.

Hyposensitization must be continued for long intervals. The minimum is at least a year and, in many cases, injections must be given for several years. Allergists vary to some extent on this point. We believe that injections should be continued until the patient is symptom-free or almost symptom-free. Then injections are stopped, but the patient or parent is warned that symptoms may return. Strict avoidance of causative allergens must continue as carelessness may result in recurrence of asthma. If symptoms do return after an interval of 3 to 10 years we advise complete re-testing. The child may have overcome certain allergens but may have acquired new ones. One must remember that an asthmatic person has an allergic foundation and therefore has the ability to change his sensitivities.[3]

II. *Symptomatic Therapy.*—

The symptomatic therapy of bronchial asthma is nonspecific and one should not expect any more than temporary relief of symptoms. The measures used, including the new corticosteroids, can only hope to lessen or eliminate the asthmatic symptoms as they occur.

Reassurance is the most important single measure, especially if the child is having his first severe attack. The calm confident manner of the physician usually exerts a very soothing influence on the frightened child and the rest of the family. The physician immediately informs everybody that the attack will be overcome within a relatively short time.

Medications are used according to the severity of the attack. For mild to moderate symptoms repeated subcutaneous injections of 1:1000 epinephrine in doses of 0.10 to 0.20 c.c. usually suffice, along with 5 to 10 drops of a saturated solution of potassium iodide. If necessary, a mild sedative may be added, e.g., elixir of Benadryl. This combination is almost always effective.

For more severe asthma, the epinephrine may be injected every 4 hours; we often add 0.10 c.c. of Sus-Phrine, a long-acting epinephrine suspension. Instillation of 5 grains aminophylline rectally is helpful and we prefer this to aminophylline suppositories. In addition, a teaspoonful of syrup of ipecac will induce vomiting, and as the child vomits he usually eliminates sputum which he has not learned to cough up in the manner of adults. Some physicians also add ephedrine by mouth.

For the most severe cases (status asthmaticus) one must usually add antibiotics, e.g., penicillin, because almost all such cases have an infectious complication which causes symptoms to continue. This diagnosis is easily made by the finding of crepitant râles as well as wheezing, also by leukocytosis, some fever, an increased sedimentation rate, and perhaps by some cloudiness in a chest x-ray film.

Hospitalization is urged for these severely ill children. Removal from the home is usually beneficial because it lessens the factor of inhalation of allergens, e.g., feathers, house dust, and animal danders. In addition, change to a hospital may be of striking benefit because of psychological factors, especially removal of the child from overprotective parents. At the hospital one can carry on investigative work, e.g., chest x-rays, blood counts, and tests of sputum for sensitivity to antibiotics. Bronchoscopic aspirations may be necessary and may be lifesaving; a nonopaque foreign body in a bronchus, e.g., peanut, pea, or bean, may be the cause of bilateral wheezing, as in a 3-year-old child recently admitted to our hospital.

Sedation in all asthmatic patients should be mild, e.g., an antihistaminic drug or aspirin. We never give morphine or Demerol to patients with asthma.

At our hospital, the Chicago Wesley Memorial, we have 12 beds for asthmatic patients. These rooms have air filters in the windows and beds with rubber or Dacron pillows and with rubber mattresses. The floor is covered with linoleum, the chairs synthetic leather, the curtains light and frequently washed. In each of these rooms there is a sign which states that feathers, flowers, and smoking are forbidden. The floors are cleaned with a wet mop.

Patients who are allergic to inhalant materials usually clear up very rapidly in such rooms. This is a fact which helps in discovering the cause of the asthmatic attack. If the asthma does not lessen in 2 to 3 days, one must question the diagnosis, or must search for other factors, e.g., allergy to foods, or some infectious process, a psychogenic influence, or a foreign body.

ACTH and prednisone have become very important. Cortisone itself is rarely used any more. In severe cases, especially in the older child and in adults, we usually start a continuous intravenous drip. Each liter of 5 per cent glucose in water contains aminophylline (about 0.25 to 0.50 Gm.) and about 10 to 20 units of soluble ACTH. The drip is continued at the rate of 2 to 3 liters per 24 hours, and this is stopped when the asthma is overcome. The child is then given intramuscular injections of ACTH-gel in doses of about 20 units per day, gradually reduced, and then stopped. In a few obstinate cases it may be necessary to temporarily substitute 5 to 10 mg. prednisone per 24 hours. In some cases the intravenous drip will not be necessary. The ACTH-gel can be injected intramuscularly.

These corticosteroids have been of great help in lessening asthmatic symptoms, but one must remember that they are not without danger, and they do not cure asthma or any other disease. The child must still be given the benefit of a thorough allergy investigation, including complete skin tests, followed by careful avoidance of causative allergens and by hyposensitization, if necessary.

Time will not permit even mention of many other available drugs, but those we have discussed are the important ones.

We would like to emphasize that asthmatic children should be as active as other children, but to the point of their breathing capacities.

Prevention of Asthma.—

Children of allergic parents frequently develop allergic conditions, including bronchial asthma. It is estimated that if both parents are allergic about 60 per cent of their children will become allergic, and about 30 per cent if only one parent is allergic.

Much can be done to lessen the chances for development of allergic symptoms in these children. Such homes should be as dust-free as possible, and they should be free from dogs, cats, feathers, kapok, and stuffed animals.

New foods should be tried one at a time, at least a week apart, to see if symptoms occur. A feeding of raw egg may be disastrous. Cooked foods are less allergenic than raw.

If mild symptoms develop, e.g., "eczema," hay fever, sniffles or recurrent bronchitis, we advise a prompt and thorough allergy survey, including complete skin tests.

Such children should be guided away from dusty occupations, e.g., farmer, furrier, baker, upholsterer, grain mill worker, florist, sandblaster, miner, or domestic.

Exposure to "colds" should be minimized.

Psychosomatic factors, if present, need proper attention.

The above precautions are important, and, if carefully followed, the onset of severe asthma in these children can be prevented, or if asthma does occur the symptoms can easily be controlled.[4, 5, 6]

The Allergy Foundation of America has now come into being. It is doing an excellent work in educating physicians and the laity and is now supporting research problems. All pediatricians should join and give a helping hand. We know a great deal about allergic diseases, including asthma. We can distinctly lessen the suffering of allergic patients.

The Jewish National Home for Asthmatic Patients in Denver, The National Foundation for Asthmatic Children in Tucson, and the Asthmatic Childrens Aid in Chicago are also of great help in this field.

DISCUSSION

In these few minutes we have briefly discussed the management of bronchial asthma in children.

In 1952, we reported our results,[2] as shown in the accompanying Table I.

We believe our results have been good. They have been even better since the introduction of ACTH and the steroids. We are not satisfied. Progress will depend on further education of the physicians and the laity. We are especially indebted to the many pediatricians who have been pioneers in the field of allergy, and who have urged early and thorough allergy surveys in suspicious cases.

The severe asthmatic child with marked pigeon breast has now become

TABLE I. RESULTS OF TREATMENT IN 306 CASES OF BRONCHIAL ASTHMA IN CHILDREN

TYPE OF ASTHMA	AGE AT ONSET	SYMPTOM-FREE		MARKED IMPROVEMENT		MODERATE IMPROVEMENT		NO IMPROVEMENT		DEAD	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I. Paroxysmal (281 cases)	Before 1	15		20		4		1		1	
	1-2	28		46		9		4		1	
	3-4	20		29		8		1		1	
	5-7	20		24		12		3		0	
	8-10	6		10		1		2		0	
	11-13	8		3		3		0		1	
	Total	97	34	132	47	37	13	11	4	4	1
II. Chronic (25 cases)	Up to 13	2	8	7	28	8	32	4	16	4	16
Total (306 cases)		99	32	139	45.5	45	14.7	15	4.9	8	2.6

almost a rarity, but we still see one occasionally, and we realize that that child has been neglected. We must renew our efforts to prevent such tragedies.

SUMMARY

Bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea, and cough. It is usually preceded or associated with seasonal or perennial rhinitis.

The responsible allergens in children are easily discovered in at least 95 per cent of the cases.

The history, physical examination, and clinical trials are important.

Skin tests should be made in all cases and be done with all protein-containing materials to which the child is exposed.

Scratch tests should be done first; intradermal tests are also necessary in about 25 per cent of all cases.

Best results are obtained by strict avoidance of causative allergens and by hyposensitization with important inhalant materials.

Preventive measures are important in children of allergic parents. They can definitely delay the onset and lessen the severity of allergic conditions, including asthma.

Reassurance, epinephrine, iodides, and ACTH and steroids are the most important symptomatic measures.

Attention to complicating infections and to psychic influences are also necessary.

Results in asthma in children are usually excellent and they are improving.

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GROWTH AND DEVELOPMENT

III. Skin Color in Negro Infants and Parents: Its Relationship to Birth Weight, Reflex Maturity, Socioeconomic Status, Length of Gestation, and Parity

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THE study of variations in skin color within the Negro group can be approached from several points of view. These may be combined into three broad categories: namely, (1) the cultural, (2) the biological, and (3) the functional approaches.

The cultural approach to the study of skin color is related to the differential values attached to being a particular color. The reaction of both Negroes and whites to this phenomenon has been the subject of a great deal of scientific observation and speculation. It is generally conceded that color plays a prominent role in Negro life. Myers and Yochelson[1] state: "Within the Negro community, shades of color have considerable social significance, and greater opportunities for enhancement of status are offered to the light-skinned individual." In a study of the skin color judgments of Negro college students, Marks[2] found that ratings of attractiveness are definitely affected by objective skin color, or by factors associated with it. Consciousness of color has been found to exist in Negro children as well as adults. Seeman[3] found that third- and fourth-grade Negro children indicate a "commitment to the superior value of light skin." He further states that skin color differences are associated with differences in "friendship and reputational status." Negro children of preschool age were studied by K. and M. Clark,[4] and the authors conclude that the factor of skin color is an important one in the genesis of consciousness of self and racial identification. These same authors[4] make two other major points:

> 1. "The results show clearly that an analysis of subjects upon the basis of skin color may not assume that the difference between the medium skin color group and the light group is equal to that between the medium and the dark group in reference to the inherent dynamics involved. . . ."
>
> 2. "It would appear that the extreme groups of light and dark children are beginning to identify themselves on the basis of their own skin color, whereas the medium group seems influenced by other factors in making identifications of self."

The problems and complications which seem to arise from this cultural evaluation of skin color have perhaps stimulated interest in the biological approach to skin color. Spencer,[5] in reporting on recent advances in pigmentogenesis, stated that the discovery of an oxidizing substance capable of bleaching pigment of the skin "opens

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vast possibilities which might have repercussions on our psychological pattern as well as on our social conduct."

The biological approach to skin color has many forms. One area of concern is the inheritance of skin color. Most authors agree that children of parents with mixed white and Negro ancestry do not themselves show any consistent pattern in skin color. Niedelman[6] states: "Children of families of mixed white and Negro blood show a wide variation in color, and in one family there may be one child almost white and another black." The same position is taken by Kephart[7] and by Dummett.[8] Kephart further states that the common anthropological estimate is that between 10 and 20 per cent of the Negroes in this country have no non-Negro ancestors.

The use of spectrophometric measurements for studying skin color inheritance has been reported on by Gates,[9] and appeared to him to suggest a promising line of study.

There is less agreement as to whether or not the infusion of "white blood" is contributing to the disappearance of Negroes as a minority group. Linton* has maintained that in 200 years the American Negro will have disappeared as a minority group. This is denied by Kephart, who feels that such a claim "does not appear to be either sociologically or biologically tenable." Blue[10] takes the position that we cannot prove or disprove whether Negroes are becoming lighter in color. The question is further complicated by general agreement that Negroes tend to grow darker with age, as indicated by Herskovits[11] and Niedelman.[6] Niedelman states that the pigmentation of the skin in a Negro does not reach its maximum until puberty, after which it decreases in intensity.

The functional approach to the study of skin color appears to have been neglected. Gross differences in pigmentation are explained in a variety of ways. Eller[12] states that, "Some authors attribute pigmentation to the effect of heat; others consider it to result from the combined effects of heat and humidity; while some believe that the color is due to the influence of the tropical sun or to increased oxygenation resulting from excessive exposure to solar rays." Whatever the reason for difference in color of the various racial groups, it would seem logical to ask if these differences have any practical effect.

Medically, the study of skin color differences has been made largely from a dermatological standpoint. Spencer[13] states that the dermatologist must recognize the play of colors and develop new visual patterns when examining cutaneous diseases in "colored people." Niedelman[6] reports that the skin of Negroes differs from that of white persons, "not only in structure and physiology but in its reaction to trauma and infection." He states, moreover, that, in addition to differences in the incidence of many diseases, there is also a difference in the "clinical and pathologic manifestations," which he feels is partly due to the social and economic conditions of Negro life.

Since the range of skin colors within the Negro group is extremely wide, this should afford an excellent opportunity to examine the practical effects of skin color *within* a racial group. The social significance of skin color within the Negro group has been widely discussed, as have also various differences between Negroes and whites in both the physical and cultural areas. From these various postulations, the next step would appear to be an examination of physical and cultural differences, if any, within the Negro group on the basis of skin color differences. To the extent that skin color represents one of the major differences between Negroes and whites, it might be hypothesized that Negroes who approach the color of white would show some differences, physical and/or cultural, from Negroes who are of darker hue. That is, it poses the question, Are Negroes a homogeneous group with regard to some measurable traits and characteristics, irrespective of skin color differences? To our knowledge, very little attention has been given to this line of analysis.

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*Cited by Kephart.[7]

It was the purpose of this study to measure some of the effects of skin color differences within the Negro group, by examining the following aspects of the problem: (1) the relationship between skin color and socioeconomic status, (2) the association between skin color of parents and skin color of infants, and (3) the relationship between skin color and some maternal-infant characteristics, namely:

(a) length of gestation period, (b) parity, (c) birth weight of infant, and (d) Reflex Maturity Index of the infant at birth.

METHODS AND MATERIALS

Data for this study are drawn from a 5-year longitudinal study of factors influencing the growth and development of Negro infants and children. Included in this segment of the Major Study are records of 661 infants and their parents. All infants were born at Hubbard Hospital between December, 1953, and September, 1956.

Selection of Participants.—Participants in the Major Study were solicited primarily from the Obstetrical Clinic of Hubbard Hospital, and through private contacts for those expectant mothers who were receiving prenatal care from a private obstetrician or physician. Only those expectant mothers who were residents of the Nashville Metropolitan area were accepted into the study. In the early stages of the project, some few persons were enrolled immediately after delivery, rather than at some time during their prenatal period.

Skin Color.—The measurement of skin color can be made on a quantitative or qualitative basis. The quantitative method is perhaps best exemplified by the use of the color top, through which a measurement of the proportion of black pigmentation in the skin is obtained. A description of the technique is available in Davenport,[14] and discussions of advantages and disadvantages of the color top method can be found in Todd and Van Gorder,[15] Bowman,[16] and Todd and associates.[17] For the purposes of this study, the color top method was impractical, due to the relatively large number of persons to be rated in a short span of time, and therefore a qualitative (color chart) method was used.

The color chart used throughout this study consists of 9 color positions, ranging from (1) Very Light to (9) Very Dark.* No provision was made for assigning a double rating to persons who fell between two consecutive color positions. Each subject was given the color position *closest* to his actual color. Positions 1-3 are considered "Light," 4-6 "Medium," and 7-9 "Dark." Skin color of the mother was obtained by using the inner aspect of the arm just above the elbow. In the majority of the cases, skin color of the father was obtained by having the mother select his color from the color chart. Before this method of obtaining father's color was adopted, a collateral study was made to test the reliability of the mother's rating. The method was found to be highly reliable, and was therefore adopted as standard procedure, since the fathers are not readily available for rating by a member of the research staff. Skin color determinations of infants at birth were made on the ear lobe.

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*Color chart drawn up, and colors reproduced by Aaron Douglas (Negro artist), Professor of Art, Fisk University, Nashville, Tenn.

Measurements of parental skin color were obtained by the medical social worker at the time when the family was accepted into the project. Measurements of infant skin color were obtained by the psychologist within 12 to 72 hours after birth, as a general rule. Before actual skin color rating was begun, the 2 persons who later assigned color ratings performed comparative ratings on the same subjects in order to ensure as much comparability as possible between ratings of parents and infants. The chart was found to give consistently reliable results when used not only by the persons who actually made the color determinations, but also by other members of the research staff who had had no training or practice in making color ratings.

Socioeconomic Status.—The index of socioeconomic status used for this study is composed of the following items:

(1) occupation of father (or mother, where necessary), (2) education of father, (3) education of mother, (4) income of father (or mother, where necessary), (5) contract monthly rent, (6) purchase price of automobile, (7) Chapin Living Room Scale,[18] and (8) modified Sewell Scale.[19]

Information on the above items was obtained by the medical social worker, especially trained for this purpose. Information on parents' occupations and education, rent and purchase price of car was obtained through interviews, and the remaining items (7 and 8) by observation in the home. The final index consists of a scale which has a range of 0-72, allotting 9 points as a maximum value for each item in the index. High scores indicate high socioeconomic status.*

When a final socioeconomic score is obtained, each family is then automatically classified into one of the 4 broad socioeconomic groupings previously found to be the most discriminating dividing points for this particular population. The limits of these groups are:

Group I:	0-14	Low
Group II:	15-29	
Group III:	30-49	
Group IV:	50 and over	High

Medical-Social Information.—The number of gestation days was obtained from the mother's hospital record, as was her parity.

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*When one or more of the 8 scalable items of information could not be obtained, or was unknown, that item was given the average point value of all of the known items. For example, if contract monthly rent was unknown (or the informant refused to give the information), and the family had a total score of 42 on the 7 other items in the Index, "Rent" was given a score of 6 (42 divided by 7), making a total score of 48. This practice was followed uniformly in order to have some rating on each of the 8 Index items.

Infant Measurements.—Physical measurements of the infants were taken between 12 and 72 hours after birth by selected members of the pediatric staff of Hubbard Hospital. Accuracy of results was verified periodically, and uniformity in technique and procedure was routinely followed. Only birth weight is under consideration here, although height, and circumference of the head and chest were also measured. No infant seriously handicapped by birth injury, congenital anomalies, or for any other cause, was included.

The reflex maturity of the infant is summarized in a Reflex Maturity Index which measures the following conditions or reflexes:

1. Activity.
2. Moro reflex.
3. Tonic neck reflex.
4. Rooting reflex.
5. Muscle tonus.
6. Ability to raise head from prone position.
7. Ability to turn head from side to side.
8. Crawling or swimming movements.
9. Stepping movements.

Each reflex is scored on a 5-point scale ranging from 0 for "Absent" to 4 for "Very Marked," resulting in an index with a range of 0-36 points.

Reflex tests on each infant were performed by the psychologist within 12 to 72 hours after the infant's birth and, as a general rule, at the same morning hour.

RESULTS

The distribution of skin color among the subjects of this study is shown in Table I.

It will be noted that for both infants and parents, the majority of the cases are classified as "medium" in color. Proportionately more adults are considered "medium," whereas proportionately more infants are considered either "Light" or "Dark." There is no consistent association of color with sex.

TABLE I. PERCENTAGE DISTRIBUTION OF NEGRO INFANTS AND PARENTS ACCORDING TO SKIN COLOR

SKIN COLOR	MALE INFANTS N = 300	FEMALE INFANTS N = 319	MOTHERS N = 647	FATHERS N = 457
1. L	-	-	-	-
2. L *Light*	1.7	3.4	0.5	1.1
3. L	4.3	4.7	4.8	4.4
4. M	18.3	16.3	16.2	11.9
5. M *Medium*	21.3	25.4	33.4	27.5
6. M	32.3	22.9	32.6	35.6
7. D	16.3	16 3	11.3	16.0
8. D *Dark*	3.7	9 7	1.2	3.5
9. D	2.0	1.2	-	-
Total	100.0	100 0	100.0	100 0

Skin Color and Socioeconomic Index.—Seeman[3] has stated that dark-skinned Negroes are found in greater proportion in the lower social class groups. This was found to be the case in our study. Table II shows the socioeconomic grouping of families according to skin color, where both parents fall into the same skin color group.

None of the "Light" parents is found in socioeconomic Group I, and none of the "Dark" parents falls into socioeconomic Group IV.

TABLE II. PERCENTAGE DISTRIBUTION OF PARENTS ACCORDING TO SOCIOECONOMIC GROUP AND SKIN COLOR*

SOCIOECONOMIC GROUP	SKIN COLOR GROUP LIGHT N = 6	 MEDIUM N = 266	 DARK N = 14
I *Low*	–	7.9	35.7
II	33.3	44.7	42.8
III	33.3	39.8	21.4
IV *High*	33.3	7.5	–
Total	100.0	100.0	100.0

*Excludes parents who are not of the same color group.

TABLE III. PERCENTAGE DISTRIBUTION BY SOCIOECONOMIC GROUP OF PARENTS OF DISSIMILAR COLOR, ACCORDING TO COLOR OF DARKER PARENT

SOCIOECONOMIC GROUP	SKIN COLOR GROUP DARKER PARENT "MEDIUM" N = 36	 DARKER PARENT "DARK" N = 101
I *Low*	2.7	5.9
II	29.7	61.4
III	37.8	28.7
IV *High*	29.7	4.0
Total	100.0	100.0

Where parents are of dissimilar color, the same trend is noted (Table III).

Proportionately more families in which the darker parent is "Medium" fall into high socioeconomic categories than do those families in which the darker parent is "Dark." When both parents are "Dark," a larger percentage will be found in socioeconomic Group I, than when only one parent is "Dark."

This lends some credence to the contention of Myers and Yochelson[1] that, "Greater opportunities for enhancement of status are offered to the light-skinned individual." It also reveals the tendency of Negroes to marry within the same color group. For the 448 families for whom skin color of both parents is available, 67.4 per cent belong to the same color group; in 21.0 per cent of the cases the mother falls into a lighter color group than the father, while the reverse is true in 11.6 per cent of the cases. Where the parents fall into dissimilar color groups, the groups are at adjacent positions on the color scale (i.e., Light-Medium, Medium-Dark) in all but one case, in which a "Light" mother is married to a "Dark" male.

There is little indication that the color of one parent is more important than that of the other parent in relation to socioeconomic status. Considering only the "Medium" mothers, their distribution among the 4 socioeconomic groups is almost exactly the same regardless of whether the mother is lighter or darker than the father (Table IV).

TABLE IV. PERCENTAGE DISTRIBUTION OF SOCIOECONOMIC GROUP OF "MEDIUM" MOTHERS, WHERE FATHERS FALL INTO A DIFFERENT COLOR GROUP

SKIN COLOR	SOCIOECONOMIC GROUP I (LOW)	 II	 III	 IV (HIGH)	 TOTAL
Mother "Medium"—father lighter	6.9	47.4	38.2	7.5	100.0 N = 173
Mother "Medium"—father darker	4.9	47.6	40.2	7.3	100.0 N = 82

Mean socioeconomic scores by skin color indicate only one major divergence in the scores of mothers and fathers in each skin color group. (Fig. 1). The mean socioeconomic score for "Dark" fathers is higher than that for "Dark" mothers, 26.9 as compared with 20.0. This is a statistically significant mean difference, although both scores still fall into the same broad socioeconomic group.

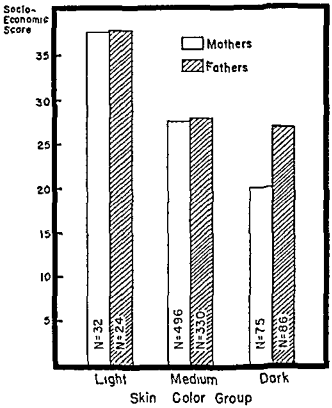

Fig. 1.—Mean socioeconomic scores of mothers and fathers, by skin color group.

A rough indication of socioeconomic status is provided by marital status, in the case of the mother. Fig. 2 shows the per cent of mothers in each color group who are unmarried. The proportion ranges from 8.8 per cent among "Light" mothers to 32.5 per cent among "Dark" mothers.

Skin Color of Parents and Skin Color of Infant.—The unpredictability of skin color inheritance among Negroes has been discussed earlier. Kephart[7] stated that, "Negro spouses whose skin color is approximately the same shade have more chance of giving birth to children either lighter or darker than themselves than do Negro spouses whose skin color is several degrees apart." Over three-fourths (76.4 per cent) of the parents in this study who belonged to the same color group gave birth to infants who fall into the same color group as their parents. Of the remaining one-fourth, 6.3 per cent of the infants are lighter than their parents, and 17.2 per cent are darker. Over 40 per cent of the infants born to parents of dissimilar color groups are in the same color group as the darker parent, while 55.5 per cent are lighter and 3.6 per cent are darker than the darker parent (Table V).

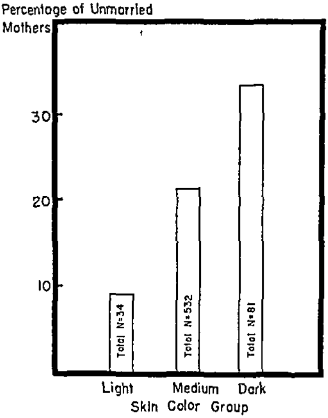

Fig. 2.—Percentage of unmarried mothers, by skin color group.

In actual numbers, 4 of the infants born to parents of dissimilar color groups are lighter than the lighter parent, and 5 are darker than the darker

TABLE V. SKIN COLOR OF INFANTS, BY SKIN COLOR OF PARENTS, IN PERCENTAGES

SKIN COLOR GROUP OF INFANTS	SKIN COLOR OF PARENTS: SAME COLOR GROUP			SKIN COLOR OF PARENTS: DIFFERENT COLOR GROUPS	
	LIGHT N = 6	MEDIUM N = 264	DARK N = 14	DARKER PARENT "MEDIUM" N = 36	DARKER PARENT "DARK" N = 101
Light	83.3	4.9	–	30.6	4.0
Medium	16.7	76.9	35.7	55.6	60.4
Dark	–	18.2	64.3	13.9	35.6
Total	100.0	100.0	100.0	100.0	100.0

parent, constituting 6.6 per cent of the total number of infants born to parents who fall into different color groups. This is considerably smaller than the proportion of infants born to parents of the same color group, who are either lighter or darker than their parents (23.5 per cent).

There is little difference between the relationship of skin color of mother with skin color of infant, and that of skin color of father with skin color of infant. This is perhaps to be expected in view of the large proportion of "same-color" marriages. Sixty-six per cent of the infants are of the same color as their mothers, and 63.2 per cent are of the same color as their fathers. The correlation coefficients for skin color of mother and infant and for skin color of father and infant are 0.3001 and 0.305, respectively.

Skin Color of Mother and Gestation Period.—Previous studies have indicated that the average number of gestation days is less for Negro mothers than for white mothers. It can therefore be postulated that lighter Negro mothers would be expected to have a longer average length of gestation than would darker Negro mothers. Fig. 3 shows the mean number of gestation days for mothers in each color group. Although the average number of gestation days decreases as the darker color group is approached, none of these mean differences is statistically significant.

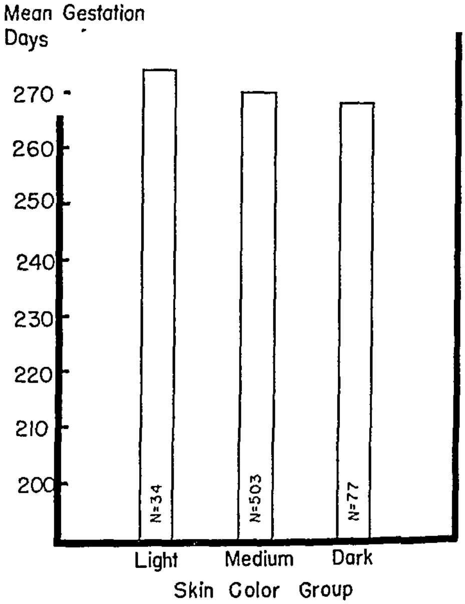

Fig. 3.—Mean number of gestation days of mother, by skin color group.

Skin Color of Mother and Parity.—Kephart[7] has stated, "It is reasonable to expect, since the differential birth rate takes the same pattern in the Negro as in the white, that the lighter-skinned Negroes have a lower birth rate than do the darker members of the group."

There is very little difference in the mean parity of mothers in this study, by skin color group. When the mean

TABLE VI. MEAN PARITY, PERCENTAGE OF MOTHERS HAVING FIRST CHILD, AND MEAN AGE OF MOTHER, BY SKIN COLOR

PARITY AND AGE	SKIN COLOR GROUP OF MOTHER			
	LIGHT N = 34	MEDIUM N = 532	DARK N = 81	TOTAL N = 647
Mean parity	2.2	1.8	2.4	1.9
Per cent having first child	20.6	27.2	19.8	26.0
Age in years	25.8	24.6	26.4	24.9

figures are rounded off, average parity is II for mothers in each color group. Actual mean figures show some slight variation which follows the same pattern as does the mean age of mothers in each color group (Table VI).

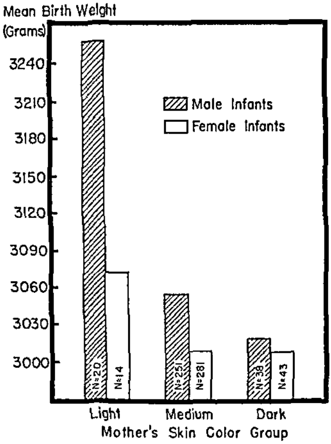

FIG. 4.—Mean birth weight of infants, by skin color group of mothers.

That is, mothers who are older at delivery also have higher average parity. The difference in average parity of "Medium" and "Dark" mothers is statistically significant. The mean age of "Medium" mothers is, however, less than that of both "Dark" and "Light" mothers. The difference in age between "Medium" and "Dark" mothers is statistically significant.

The percentage of mothers who were having their first child at the time of this study is nearly equal for "Light" and "Dark" mothers, but is about one and one-third times as high for "Medium" mothers. This is a statistically *significant difference, but it too* must be evaluated by taking into consideration the difference in age of "Medium" and "Dark" mothers.

Skin Color of Mother and Birth Weight of Infant.—Mean birth weights of infants by skin color of mother are shown in Fig. 4.

The difference between mean weights of infants born to "Light" mothers and infants born to "Dark" mothers is significant for both male and female babies. The correlation coefficients for skin color of mother and birth weight of *infant are +0.0719 and −0.0576* for male and female infants, respectively, and are not statistically significant. Thus, there appears to be some relationship between mother's skin color and birth weight of infant when skin color is considered on the basis of color *group,* but not when the individual color ratings are used.

Skin Color of Infant and Birth Weight.—No relation is apparent between skin color group of infant and birth weight. For both male and female infants, the heaviest mean birth weights occur in the following order, according to skin color: (1) Dark, (2) Light, (3) Medium (Fig. 5).

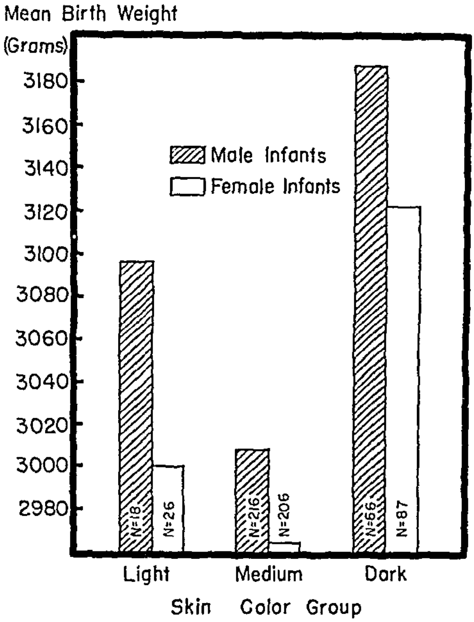

Fig. 5.—Mean birth weight of infants, by skin color group.

Skin Color of Infant and Reflex Maturity Index.—Previous studies dealing with newborn reflexes have indicated that, on the average, reflexes can be elicited from female infants to a greater degree than from male infants. Since this suggests that there is some difference among infants in the maturity of reflexes at birth, the relationship between reflex maturity at birth and other hereditary factors might logically be investigated.

No relationship is apparent between skin color group and reflex maturity for male infants, but among female infants mean reflex maturity index increases as the darker color group is approached (Fig. 6).

The difference between the means of "Light" and "Dark" female infants is not, however, statistically significant, and in the absence of a corresponding trend among male infants, may suggest coincidence rather than a significant relationship.

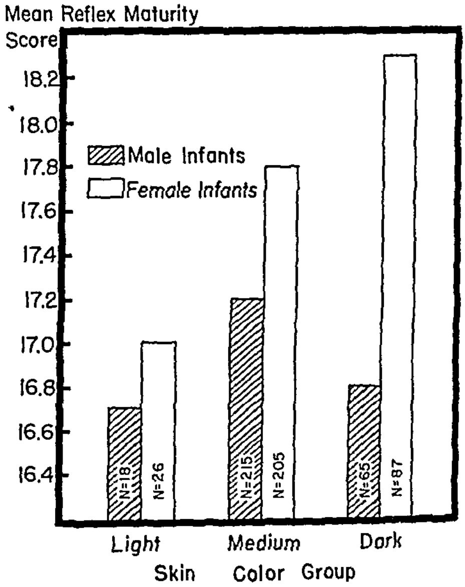

Fig. 6.—Mean Reflex Maturity scores of infants, by skin color group.

SUMMARY AND CONCLUSIONS

From data presented in this study, it is apparent that there are some areas in which specific relationships can be observed between skin color and other factors, among Negroes.

1. The social significance of skin color is confirmed not only by the greater proportion of dark Negroes in the lower socioeconomic groups (68.7 per cent of the families in which one or both parents were dark are found in socioeconomic Groups I and II, as compared with 49.8 per cent of the families in which the darker parent is medium, or both parents are medium), but also by the greater proportion of dark mothers who are unmarried. About four times as many

"Dark" mothers are unmarried as are "Light" mothers. It cannot be said whether or not the latter relationship reflects merely preferential marriage wishes, less feeling of obligation to marry women of low socioeconomic status, or some other factor or combination of factors.

2. No conclusion can be drawn concerning the inheritance of skin color from a superficial study, since the skin color of children appears to be influenced both by parents and by ancestors farther removed than parents. Results of this study indicate that the majority (in this instance, three-fourths) of children born to parents of the same color group fall into the same color group as their parents, while slightly more than half of the children born to parents of different color groups are lighter than the darker parent. There is general indication that the vast majority of Negro infants in this study are neither significantly lighter nor darker than their parents.

3. A definite relationship is seen to exist between birth weight and mother's skin color, with lighter mothers tending to have heavier babies. This relationship is evident, however, only in terms of skin color *group*.

4. Other characteristics associated with the birth of infants, specifically length of gestation period and parity, have no such clear relationship with mother's skin color. Although the mean number of gestation days decreases consistently as the darker color group is approached, the mean differences are not statistically significant. There is a significant difference in the parity of "Medium" and "Dark" mothers, but this difference is paralleled by a similar difference in the mean age of mothers in these two groups.

5. There apparently is no consistent relationship between the skin color of the infant at birth and his weight at birth, nor does his skin color appear to be significantly related to reflex maturity at birth.

Whether or not Negroes are a homogeneous group, irrespective of skin color differences, cannot be stated categorically. Skin color does seem to have definite cultural and biological significance. Its functional significance is perhaps less certain. The only clear relationship of a functional nature indicated by this group is that existing between skin color group of mother and birth weight of infant. Here the associations between socioeconomic status and skin color, and socioeconomic status and birth weight must be borne in mind. The relationship between socioeconomic status and birth weight for this study population is discussed by Crump and his associates.[20]

It is conceivable that any functional significance which skin color may have is closely related to the social significance which skin color has among Negroes; i.e., light color is generally associated with high socioeconomic status, and high socioeconomic status is in turn associated with such factors as heavier average birth weights and longer gestation periods.

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THE PREVENTION OF BILIRUBIN ENCEPHALOPATHY

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The treatment of hemolytic disease of the newborn is concerned with the reduction of infant mortality and the prevention of bilirubin encephalopathy.[1] The latter has become the focal point in recent years and, as a result, many articles have been written describing criteria for replacement transfusions. Considerable latitude exists and seems to depend in part on the particular discipline of the writers. The present paper is concerned with a review of the authors' experiences in the management of this problem based on the conviction that bilirubin is toxic to the newborn brain.[2-6] Since this toxicity is closely related to the serum bilirubin level, the capacity of the infant to handle bilirubin as reflected by the latter was used as the principal criterion for replacement transfusion. A high cord level with a rise of serum bilirubin toward critical levels (20 mg. per cent)[7] early was interpreted to indicate impaired capacity and thus dictated the need for early replacement transfusion to prevent brain damage. Significantly, in a number of cases, bilirubinemia of this degree did not develop and thus management without transfusion was elected with good clinical results. Maternal titer and/or a positive Coombs' test by themselves were indicative of sensitization in the mother and potential active disease in the newborn, respectively, but, in the absence of obvious clincal disease, were not considered indications for immediate transfusion; nor was prematurity or past history by themselves, although it was recognized that these were additional hazards which mandated careful evaluation and close surveillance of the infant.

MATERIAL

The cases studied were confined to instances of Rh incompatibility with a positive Coombs' test during a 4-year period from January, 1953, to December, 1956, in a 250-bed hospital (Table I). Cases transferred from outside hospitals are not included in this series. During this period there were 10,876 deliveries of which 65 infants were diagnosed as showing evidence of Rh incompatibility, an incidence of one of 152 births. This figure is not dissimilar to the general average of 1 in 200 quoted by Diamond[8a]; the difference may be explained by the referral of sensitized mothers to this hospital which serves as a center to which complicated cases are referred. However, there were only 6 stillborn infants (9.2 per cent) which is considerably lower than that quoted by Allen and Diamond[9] and no ready explanation is available. The remaining 59 were liveborn but 3 died within a few hours of birth, one

TABLE I
(JANUARY, 1953 - DECEMBER, 1956)

Total deliveries	10,876
Rh incompatibility	65 cases (1-152)
Stillborn	6 cases (9.2%)
Liveborn (Coombs' positive)	59 cases
Mortality	
1. Immediate - no replacement transfusion	3 cases (5.0%)
2. Replacement transfusions	4 cases (6.8%)
a. Brain damage	2 cases (3.4%)

with bilateral polycystic kidneys, the other 2 with severe hydropic disease without a replacement transfusion being attempted.

This report concerns itself mainly with the remaining 56 infants who were liveborn. Since the philosophy of management varied somewhat in these cases, it is necessary to further subdivide them into two groups to evaluate them properly from the points to be established. Thirty-one were supervised by the author using the criteria as outlined previously. The remaining 25 cases were supervised by other staff members who tended to use the more liberal accepted criteria in the literature.

TABLE II. MATERNAL TITER IN RELATION TO MANAGEMENT IN EACH SERIES

	TITERS	1-1	1-2	1-4	1-8	1-16	1-32	1-64	1-256
Author	Conservative			4		2		5	
	Exchange	1		1		6	1	5	4
Other	Conservative	1		1		1			
	Exchange	2		3		5	1	8	4

The relationship between maternal titer and management in each of the above groups is shown in Table II. Titers were recorded in all but 1 case. It is seen that there is considerable variation between height of titer and management. In the author's group, where titer alone was not used as a criterion, 7 of the 11 with titers of 1-16, or greater, were managed without transfusion, while in the other groups only 1 in this range was treated in this manner. Disregarding titer alone, it was possible to manage 11 (35.5 per cent) without transfusion which compares favorably with 36 per cent quoted by Walker and Neligan[10] in a much larger series of 264 cases. In the other group, where it would appear more emphasis was placed on maternal titer, only 4 (16 per cent) were treated without transfusion. All of the infants so treated in both groups are free of sequelae after follow-up at the present time.

The pertinent clinical details of the infants managed without transfusion are illustrated in Table III. It will be observed that in 8 cases there was no detectable jaundice during the hospital course and in the remaining 7 the earliest onset was at 12 hours of age with the majority at or after 24 hours of age. In addition, there was almost a complete absence of other signs of clinical disease in these cases. Of interest also is the variation in hemoglobin values at birth which ranged between 13.0 Gm. per 100 c.c. and 19.5 Gm. per 100 c.c.

TABLE III. CONSERVATIVE CASES

				SERUM BILIRUBIN LEVELS						
CASES	BIRTH WEIGHT	CLINICAL JAUNDICE	ONSET (HR.)	CORD MG. %	PEAK RECORDED MG. %	AGE AT PEAK (HR.)	TITER	PREG-NANCY	HGB. AT BIRTH GRAM %	CLINICAL DISEASE
1	7^{10}	None	--	--	6.2	24	1-16	VI	15.5	None
2	7^{0}	None	--	0.4	0.8	24	1-64	III	15.0	None
3	7^{8}	Present	24	1.9	10.0	48	1-64	IV	13.0	None
4	9^{5}	None	--	--	--	--	1-64*	I	--	None
5	7^{13}	Present	<24	3.9	15.8	72	1-64	III	14.0	None
6	5^{8}	Present	18	2.3	12.2	72	1-4	V	19.3	Liver and spleen 2 F ↓†
7	6^{11}	None	--	1.4	3.2	24	1-4	III	16.0	None
8	9^{1}	Present	72‡	2.3	9.5	50	1-64	V	16.0	Liver 2 F ↓
9	7^{4}	Present	24	1.6	5.0	48	1-4	VI	14.5	None
10	6^{13}	None	--	1.4	2.2	16	--	III	15.0	None
11	7^{10}	None	--	--	5.0	72	1-64	IV	13.5	Liver and spleem 1 F ↓†
12	8^{14}	None	--	1.1	3.8	48	1-16	IV	15.8	None
13	7^{2}	None	--	1.5	4.1	15	1-16	IV	14.5	None
14	6^{15}	Present	12	--	11.9	28	1-1	V	18.8	Liver and spleem 1 F ↓†
15	5^{10}	Present	72‡	2.2	8.2	50	1-4	III	16.0	None

**Three previous transfusions Rh positive blood.* (?)

†Fingerbreadths palpable below costal margin.

‡Clinical observation in chart.

In the combined replacement groups, there were 4 deaths (7.1 per cent) all in severely diseased infants which compares favorably with 6 per cent quoted by Walker and Neligan.[10] Two of these died at 48 hours of age and, at post-mortem examination, extensive pulmonary hemorrhage was found in addition to severe erythroblastosis fetalis. One died at 24 hours of age and showed generalized edema in addition to severe erythroblastosis fetalis. Although none of the above 3 infants showed straining of the brain, the fourth one demonstrated this at post-mortem examination.

The clinical and laboratory details of the last case deserve additional comment and are further illustrated in Fig. 1. This mother had been followed through two previous pregnancies with elevated titer (1-64) and, although the Coombs' test was positive in each instance, the infants were managed successfully without transfusion since at birth there were no significant signs of clinical disease and bilirubinemia of sufficient degree did not develop early. In this fifth pregnancy, the titer rose to 1-256 and, at birth, marked signs of disease were present, including pallor, hepatosplenomegaly, and ecchymoses. The initial replacement transfusion was done at 2 hours of age and yet the serum bilirubin continued to rise despite three subsequent transfusions. The significance of this rise is more readily appreciated when the hemoglobin value obtained at birth is noted (6.7 Gm. per 100 c.c.). Using the arbitrary value of 17.6 Gm. per 100 c.c. as a normal value[8b] and disregarding new blood formation, the minimum destroyed hemoglobin would be 17.6-6.7 or 10.9 Gm. per 100 c.c. Accepting 300 c.c. as the total blood volume, the minimum amount of destroyed hemoglobin would be three times 10.9 Gm. or 32.7 Gm. The latter must have taken place in utero and was deposited in the fetal tissues. Thus, a large reservoir existed which served as the source of bilirubin even though early and repeated replacements had been accomplished. Watson[11] states that potentially 34.7 mg. of bilirubin may be derived from 1 Gm. of hemoglobin. In this instance then more than 1 Gm. of bilirubin may have been presented to the infant for clearance which he was incapable of doing before brain damage occurred.

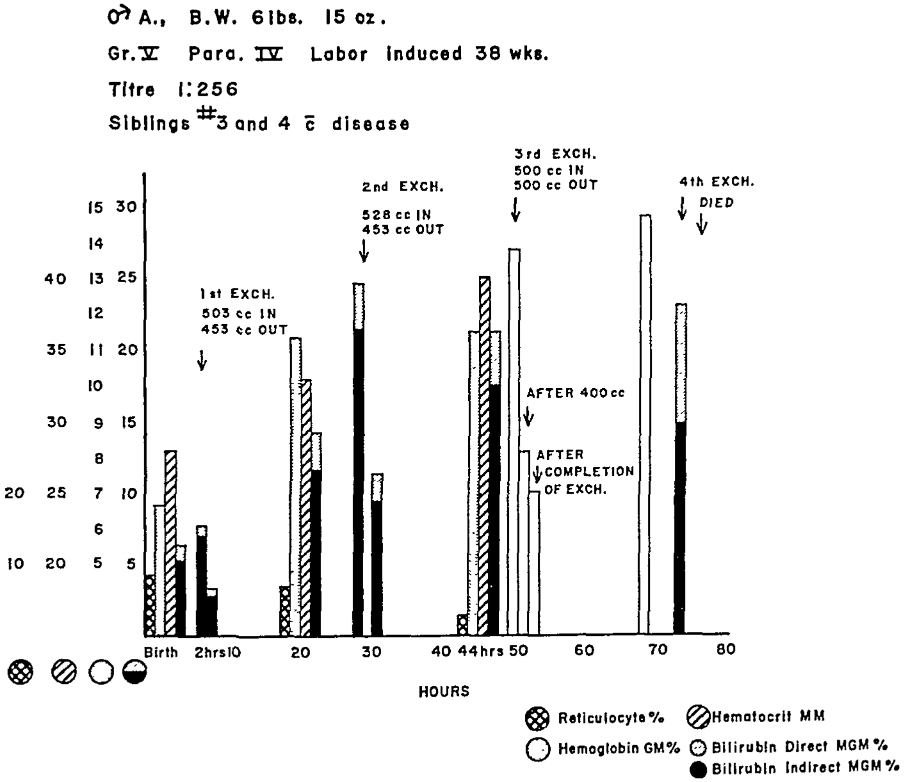

Fig. 1.—Hematological data as illustrated except open bars at 50 and 70 hours represent total bilirubin mg. % without the separate fractions being determined at these intervals.

The exchange transfusions accomplished the removal of only a small fraction of this amount[12] and, thus, the majority was left to be conjugated by the liver. The impairment of glucuronide production and conjugation noted in newborn infants,[13] therefore, contributed further to the high serum levels of indirect bilirubin and the complication of brain damage.

The second case of brain damage did not occur in the author's group and probably resulted in part from laboratory error in the bilirubin determination and thus might have been prevented. Accuracy in this procedure is obviously of the utmost importance to the clinician charged with the responsibility of these cases. Correlation with the clinical appearance of the jaundice may be difficult and in any event must be based on clinical judgment. However, this case re-emphasizes further the significance of scrutinizing laboratory reports in relation to clinical appearance in order to evaluate them properly. Whenever there is disagreement, immediate recheck is essential.

Re-exchanges were done primarily when the serum bilirubin continued to rise toward critical levels (20 mg. per cent) and the time for peak levels had not passed, namely, usually after 3 days in the full term and not until the fourth to sixth day in premature infants.

DISCUSSION

Although reduction in infant mortality is to be desired, a significant percentage of infants with hemolytic disease of the newborn due to Rh incompatibility will be either stillborn or hydropic and severely ill at birth. These are usually not salvageable with current management and pose a problem for further investigation and improvement.

At the present time, therapy is primarily effective in preventing bilirubin encephalopathy in those infants who develop jaundice early and, subsequently, if left untreated, may develop this serious complication of brain damage.

The course of management followed by the author in the previously described cases was established following the identification of the pigment within the cytoplasm of the brain cell as bilirubin.[2, 3] In this connection, it is important to re-emphasize that although in those investigations other heme pigments were identified in the peripheral blood,[2] bilirubin was the only pigment demonstrable in the brain cells. Subsequent studies strengthened the conviction of bilirubin toxicity. Staining of the brain was produced in newborn rats by the injection of a bilirubin solution indicating significant biochemical and physiologic differences in this age period.[4] The latter were in part highlighted by the demonstration in vitro of a striking reduction in oxygen uptake in newborn rat brain hemogenates as compared with adult brain homogenates[5] and the localization of inhibition at the level of the pyridine nucleotides.[6]

Most recently, glucuronic acid production in newborn and premature infants was demonstrated as variable and less than in adults and conjugation in the immediate newborn period impaired. Therefore, the serum bilirubin level reflects best the potentiality of any given infant for brain damage. Admittedly better measurements are needed for assessment of the latter and continued investigation into this aspect of the problem is needed.

It should also be borne in mind that other factors may be additive in terms of toxicity. Crosse and Meyer[14] and Allison[15] have suggested that vitamin K in large doses leads to an increased incidence of brain damage in premature infants and Silverman and associates[16] reported an increased incidence in prematures with routine prophylaxis using Gantrisin and penicillin. In the light of recent studies we may speculate that these and other, as yet unidentified, substances may be additive by various mechanisms in terms of toxicity at the cellular level in the newborn infant.

Those infants who are clinically free of disease and have only a positive Coombs' test at birth, regardless of maternal titer, should be watched closely for signs of jaundice; if this occurs early, particularly within the first 12 hours of life, replacement transfusion is indicated. In this connection it should be re-emphasized also that the development of bilirubin encephalopathy is usually between the third and fifth day of life[17] which corresponds with the peak serum bilirubin levels. The earliest recorded occurrence is at 18 hours of age[18] and, therefore, in general there is time for careful evaluation in an otherwise well infant.

Those infants with obvious clinical signs of disease at birth should be subjected to replacement transfusion promptly, but it should be recognized that the presence of edema carries a very poor prognosis for survival.

However, it is our observation, as well as others, that a significant number of infants who do not fall into the above classifications will do well without a replacement transfusion and thus need not be subjected to the hazards of this procedure which include sepsis, trauma, and thrombocytopenia. The latter may be magnified in unskilled hands.

In those cases requiring intervention, the incidence of brain damage should be extremely low. In rare cases, the load of bilirubin may be so great that present-day techniques are not sufficient to prevent encephalopathy.

SUMMARY

1. Maternal titer values and/or a positive Coombs' test by themselves are not an indication for replacement transfusion in hemolytic disease of the newborn due to Rh incompatibility. The main emphasis should be placed on the clinical condition and early course of the newborn infant, particularly the ability to handle bilirubin.

2. A demonstrated rise of serum bilirubin toward critical levels (20 mg. per cent) early, particularly within 12 hours, remains the best single criterion for the need of replacement transfusion in questionable cases. Close supervision is essential.

3. Clinical judgment, which requires a thorough understanding of the clinical and laboratory data, may indicate the necessity of transfusion in individual cases. Therefore, it is desirable to refer these infants to a Center if adequate facilities and personnel are not available. The procedure itself is not without hazard, particularly in the hands of unskilled personnel.

4. Replacement transfusions by present methods may be inadequate, in rare instances, to control the serum bilirubin level and prevent brain damage.

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A Danger of Vaccination

June 27, 1857.—Dr. Buck reported two cases of *Erysipelas following Vaccination*. They were novel to him, and might be interesting to the Society.

In March last, he vaccinated a child a few weeks old, and at the end of a week a good vesicle had formed; there was no areola. He charged some quills, and supposed that everything would go on according to the rule. The third day after this, the child was attacked with erysipelas about the pustule, which soon involved the whole arm, and extended to the chest, running its course very rapidly. Death ensued on the eighth day from the time when the disease was first seen. He vaccinated several children with matter taken from this child, and they all did well.

On the 4th of the present month, he vaccinated a healthy child, also a few weeks old, and on the seventh day charged his quills. Nine days after this, the sixteenth day after the vaccination, erysipelas appeared on the arm, ran down the chest, abdomen and the legs; this patient is now recovering. He also vaccinated several children with lymph taken from this case, and no trouble had as yet ensued.

There was no case of erysipelas in the houses where either of these children were living, and no predisposition to this disease, as far as he knew, in either of the families to which they belonged. These are the only cases of the kind Dr. Buck has ever met with.

Extract from the RECORDS OF THE SUFFOLK DISTRICT MEDICAL SOCIETY, THE BOSTON MEDICAL AND SURGICAL JOURNAL, Feb 4, 1858.

THUMB- AND FINGER-SUCKING: A STUDY OF 2,650 INFANTS AND CHILDREN

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MUCH has been written on the various phases of finger- and thumb-sucking by pediatricians, psychiatrists, psychologists, dentists, and orthodontists. Even lay publications have devoted much space to this debatable subject. However, few statistical studies have been made of this habit in healthy infants and children.

Roberts[1] investigated 30 infants between 7 and 8 months of age; 15 sucked their thumbs, and 15 did not suck their thumbs. She obtained information pertaining to the type of feeding; number of feedings per day; changes in feeding schedule; time per feeding; and onset of thumb-sucking. The majority began to suck their thumbs during the first 3 months of life. None of these infants used a pacifier. It was concluded that non-thumb-suckers spent a longer time per feeding than those babies who sucked their thumbs. This is in agreement with Levy's[2-4] observations that the amount of time spent in sucking is the primary determinant of the finger- or thumb-sucking habit.

Brazelton[5] evaluated 70 healthy infants regarding the occurrence of extranutritional sucking. Sixty-one exhibited an appreciable amount of sucking, which was satisfying to the infant. Onset was from birth to 3 months of age, with increasing intensity to 7 months of age. At this time thumb-sucking began to decrease. Only 4 infants continued to suck their hands at 1 year of age. Past 2 years of age, only 2 infants continued this habit. He stresses "the importance of extranutritional sucking as a source of gratification in infancy. Its occurrence is normal and its disappearance is spontaneous in most infants when not inhibited." This latter statement is in agreement with what has been previously written.[6, 7]

Klackenberg[8] reported, his experiences with 259 children between 4 and 6 years of age. Of this group, 50 per cent had been thumb-suckers. At 1 year of age, 50 per cent of the 129 infants who sucked their thumbs persisted with this habit; 47 per cent were sucking their thumbs at 2 years of age. The percentage of those who persisted with this habit gradually decreased over the years, until only 21 per cent of the 129 children sucked their thumbs at 6 years of age. In 100 cases he established the onset of the habit as follows: prior to 3 months of age, 54 per cent; 3 to 5 months of age, 22 per cent; 6 to 9 months of age, 14 per cent; after 9 months, 10 per cent. There was no significant difference in the incidence of thumb-sucking among breast-fed infants. He found an equal number of children who sucked and did not suck their thumbs among those who were fed for 20 minutes as well as those who were fed for shorter periods.

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METHOD OF STUDY

It was the purpose of this study to investigate finger- and thumb-sucking and specific factors that we thought were pertinent to this habit. When we use the term "thumb-sucking" it will mean "finger- or thumb-sucking." Thumb-sucking as discussed in this paper refers to placing the thumb or fingers deep into the mouth many times every day and night and exerting definite sucking pressure. A total of 2,650 infants and children were selected in consecutive order from a general pediatric practice. All patients were Causasian and came from the middle socioeconomic group of our population. None of these infants or children had any chronic or congenital diseases that could alter their feeding habits. They ranged in age from birth through 16 years.

The mother of each patient was questioned verbally, by use of open-end questions, regarding feeding habits, whether the baby sucked his thumb or not, the age of onset and termination of this habit, length of time of feedings, and other factors that will be discussed later. We urged each mother to keep a record of length of time of feedings. We checked these items in our infants during monthly visits the first year of life, quarterly visits the second year of life, and semiannual visits thereafter. All patients were followed from birth, and the parents were questioned in the same way regarding this habit, beginning with the infant's first visit to us. One of us (A. S. T.) followed many of these patients until they were 17 years of age. The parents were not told they were being included in a study of thumb-sucking. Parents who could not be specific in their answers or remember certain items were not included in this study. We did not ask the questions in a leading manner or solicit answers. Every effort was made to be as objective as possible.

All infants were on a demand feeding schedule and averaged six feedings per day for the first 3 months of life. A few infants took 5 or 8 feedings per day during this period.

In the older children, special attention was given to the examination of the mouth, the incidence of malocclusion, and whether or not the patient was receiving orthodontic care.

RESULTS OF STUDY

1. A total of 2,650 patients was studied; 1,340 were male, and 1,310 female.

2. There were 1,208 thumb-suckers, 45.6 per cent of the total group. Of these, 596 were male and 612 female. Since the sex distribution is not statistically significant, further breakdown of groups according to sex will be omitted. Seventy-five per cent of the infants who sucked their thumbs began to do so during the first 3 months of life, and the other 25 per cent during the remainder of the first year of life. We frequently noticed thumb-sucking in the newborn nursery and during the neonatal period.

3. Three hundred infants (11.3 per cent of total group) were partially or completely breast fed. Average duration of this type of feeding was 4.4 months. Of this number, 130 (43.3

per cent) sucked their thumbs. Breast feeding was not found to be a significant factor in the incidence of thumb-sucking.

4. The majority of our patients took less than 30 minutes to feed. Of the patients in the "fast" and "average" group, 41.7 to 45.8 per cent were thumb-suckers (Table I). This is probably significant. The higher incidence of thumb-sucking, 62.7 per cent, in the "slow" group will be discussed later.

TABLE I

FEEDING TIME (MINUTES)	NO. IN GROUP	PER CENT OF TOTAL GROUP	THUMB-SUCKERS	
			NO.	PER CENT
10 or less ("fast")	524	19.7	240	45.8
15-25 ("average")	1,639	61.9	683	41.7
30-60 ("slow")	419	15.8	263	62.7
60 or longer	68	2.6	22	32.3

5. The average age at which all thumb-sucking stopped was 3.8 years. A few stopped during infancy, and some as late as 12 to 15 years of age. Most parents expressed minor concern about this habit during the first 2 to 3 years of age. As the habit persisted past 3 years of age, their anxiety increased.

6. Pacifiers were not recommended. Of 28 patients who used them, 8 sucked their thumbs.

7. Malocclusion was diagnosed by us if there was a protrusion of the anterior upper teeth with a normal molar relationship, or if there was a protrusion of the maxilla with an abnormal molar relationship of the first maxillary molar being one-half tooth forward from the normal position. Patients were then referred for orthodontic care. If the orthodontist concurred in our findings, the patient was classified as having malocclusion. Malocclusion occurred in 211 patients, or 7.9 per cent of the total group. Of these children, 117, or 55.4 per cent, sucked their thumbs. Of 86 children who wore braces for malocclusion, 53 had never engaged in the sucking habit and 33 sucked their thumbs. This is not statistically significant. Of thumb-suckers, 9.7 per cent developed malocclusion, compared to 6.5 per cent of the nonthumb-suckers. There is a highly significant difference between these two percentages, pointing to a definite effect of thumb-sucking on malocclusion. The degree of relationship between thumb-sucking and malocclusion, though statistically significant, is obviously very small and of limited extent. However, there is clearly some relationship. One reason for this may be that thumb-sucking beyond a critical age only will result in malocclusion. This is a theoretical possibility, but it is being studied. It is interesting to note that 4 children had mechanical devices placed on their molars to break the sucking habit. This was successful with 1 child and failed with 3 children. More psychological distress was observed in these latter children after insertion of the dental bar than was seen during the thumb-sucking period.

8. Psychological problems in the children were diagnosed as such if there was an inadequate adjustment to their environment. This was evaluated with respect to school and learning difficulties as reported to parents by the teachers; poor peer relationship as noted by parents and/or friends; enuresis without organic pathology; night terrors; excessive sexual interest as manifested by masturbation; and food fads producing obesity or poor nutrition. Psychological problems occurred in 137 patients, or 5.2 per cent of the total group. Of these 137 patients 67 (49 per cent) sucked their thumbs. There was no statistical relation between psychological problems and thumb-sucking.

9. Two hundred and eighty-two infants, 10.6 per cent of total group, had colic. One hundred and twenty-nine of these babies, 45.7 per cent, sucked their thumbs. There was no relationship between colic and thumb-sucking.

10. Of the 1,208 patients who sucked their thumbs, 976, or 80.8 per cent, still persisted with this habit at 2 years of age. Only 48 infants, 3.9 per cent of those who sucked their thumbs, stopped this habit prior to, or at, 1 year of age. There are 96 infants 1 year of age at the time of writing who are still sucking their thumbs.

TABLE II

	TOTAL	SUCKED THUMB		DID NOT SUCK THUMB	
		NO	%	NO.	%
Total group	2,308	1,037	44.9	1,271	55.1
Siblings	1,447	646	44.6	801	55.4
Nonsiblings	861	391	45.4	470	54.6

11. We were unable to find any significant difference in the thumb-sucking habit between only children and those with 1 to 4 siblings (Table II). Three hundred and forty-two children were omitted from this part of the study because of lack of follow-up of the patient and/or siblings. There was also no significant correlation of this habit among identical and fraternal twins, and between twins and one or more siblings. One cannot say that identical and fraternal twins will have similar thumb-sucking habits.

DISCUSSION

To our knowledge, this is the largest series of patients reported that has been statistically analyzed. Of our 2,650 infants and children, 45.6 per cent sucked their thumbs. There was no sex difference, which is contrary to Gesell and Ilg's[7] observation that more boys than girls suck their thumbs. Breast feeding was not a significant factor in the incidence of thumb-sucking.

Feeding time was probably significant in the incidence of thumb-sucking. The majority of individuals in our study, 81.6 per cent of the total group, took 30 minutes or less to feed. Of patients in the group of "fast" and "average" feeders, 41.7 to 45.8 per cent sucked their thumbs (Table I). Bakwin[6] believes that inadequate sucking time as a cause of thumb-sucking is of minor importance.

Of interest is that there was a significantly higher incidence of thumb-sucking in infants who fed 30 to 60 minutes. Our opinion is similar to Pearson's,[9] namely, that stimulation of the lips and mouth, which are richly supplied with sensory nerve endings, gives a marked feeling of pleasure. Once this satisfying sensation is experienced, there is a desire to have it repeated. Therefore, the more a baby sucks, the more the oral structures are stimulated, and the more gratification is obtained. On this basis the infant would tend to suck his fingers or thumb because the pleasure he derives has been so implanted and developed. The baby who spends less time for nutritional sucking does not have this pleasure so strongly developed because there is less oral stimulation, and he may not suck his thumb. Sears and Wise[10] showed that the oral drive is strengthened by the longer retention of the sucking method of feeding. Therefore, a substitute sucking habit would increase with a decrease in nutritional sucking. The strength of the oral drive, and not frustration in weaning, would determine the incidence of thumb-sucking.

The smallest percentage of those who sucked their thumbs was in the group that took 60 minutes or longer to feed. We cannot offer a suitable explanation for this.

The average age at which the thumb-sucking habit stopped spontaneously was 3.8 years. This is longer than the 2-year limit that has been mentioned in the literature. However, dentists say that cessation of the habit at this age is compatible with normal tooth and dental arch formation. If malocclusion is caused by the thumb-sucking, the displaced teeth and arch will spontaneously correct themselves after the sucking has ceased, especially after development of permanent dentition.[11-16] Ruttle[16] states that "the effect of thumb and finger habits on the molar occlusion merely approaches statistical significance, and does not attain clinical utility."

Of the 211 patients who had malocclusion, 117 sucked their thumbs (9.7 per cent of all thumb-suckers). Of 86 children who wore braces, only 33 sucked their thumbs. This is not significant. Johnson[17] studied 989 cases of malocclusion and found 173 patients (17.5 per cent) who sucked their thumbs. In 24.5 per cent of the thumb-suckers, the habit persisted one year or less. Sixty per cent had broken the habit by the end of the third year. According to an editorial[18] that most adequately summarized the topic of thumb-sucking, when one considers thumb-sucking as a whole, it is a rare cause of dental deformities. We are in disagreement with those[19-21] who maintain that forceful measures should be instituted to stop this habit because of possible dental malformations and psychological problems.

Dental devices to stop thumb-sucking were not used in enough cases to be truly evaluated. We found that the habit terminated spontaneously in the great majority of patients, and at an early enough age so that routine use of such a bar was not the usual procedure. Indications for the use of a dental bar, and the related problems, are discussed by Graber.[15]

There was no correlation between colic and thumb-sucking.

Twenty-eight patients used a pacifier, of whom 8 sucked their thumbs. This small number cannot be statistically evaluated. However, we have seen patients, who did not suck their thumbs while using a pacifier, begin this habit when the pacifier was discontinued.

Klackenberg[8] observed no thumb-sucking in 28 infants who used a pacifier over 3 months. Starr[22] prefers the pacifier to the thumb, from the orthodontist's standpoint. He believes a child can be more easily separated from the pacifier than from his thumb. Rittelmeyer[23] investigated 364 children to determine the value of the pacifier in the prevention of thumb-sucking; 87 children sucked their thumbs and 54 used pacifiers. Among those who did not use pacifiers, 27 per cent were thumb-suckers. Of the 54 who did use them, only 8 sucked their thumbs. Of these, 5 were thumb-suckers before pacifiers were instituted. In only 3 instances did the pacifier fail to prevent thumb-sucking. Only 14 children in this study stopped the sucking habit by the time they were 2 years of age, and 12 continued it after 7 years of age. However, only one child used a pacifier past the age of 2 years.

No correlation was found between psychological problems and thumb-sucking. Most authorities are of the opinion that the great majority of thumb-sucking stops spontaneously around 2 or 3 years of age and that forceful cessation of the habit will create neurotic symptoms and personality problems which are more serious than the sucking habit.[6, 7] One definitely cannot predict psychological problems because a child has been or is actively engaged in thumb-sucking. Kaplan[24] believes that thumb-sucking that persists after the usual time for disappearance is a symptom of emotional disturbance for which the treatment must be based upon the etiology. Persistence of the habit may be due to boredom, fatigue, or unhappiness.

We are in agreement with others[6, 25, 26, 27] that the problem of thumb-sucking has been overemphasized and parents unduly alarmed. Parents should be informed and reassured about the relative harmlessness of this habit. Occasionally, it may continue because it has been established as a habit even though most of the psychological implications have disappeared.

Our findings differ from that of previous reports[5, 8] that the majority of patients who sucked their thumbs stopped by 1 or 2 years of age. In our study, 80.8 per cent of those who sucked their thumbs persisted at 2 years of age, while 3.9 per cent of those who sucked their thumbs stopped at 1 year of age or earlier. These figures are close to Johnson's[17] results. From our findings it would appear incorrect to tell anxious parents that their child will stop this sucking habit by 1 or 2 years of age.

SUMMARY

A study of finger- and thumb-sucking and related factors in 2,650 infants and children has been statistically analyzed and clinically evaluated. The pertinent literature has been briefly reviewed.

The authors wish to express their thanks to Dr. Thomas Baffes for his analysis of the statistics utilized in this study.

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MONALDI DRAINAGE IN THE MANAGEMENT OF POSTINFECTIOUS PULMONARY CYSTS

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WITH the striking decrease in pneumococcic infections since the introduction of antibiotic drugs, there has been a relative increase in the incidence of staphylococcic pneumonia.[3, 7] Concurrently, there has been an increase in the incidence of staphylococcic empyema, spontaneous pneumothorax, and postinfectious air cysts. It is estimated that these air cysts (also called pneumatoceles, postinfectious bullae, or blebs, the term depending on size and location within the lung) occur in 25 per cent of the cases of staphylococcic pneumonia.[6] Continuous closed drainage in the treatment of empyema and spontaneous pneumothorax is universally accepted,[1, 2] but opinions differ as to its use in management of postinfectious air cysts. These cysts are usually thought to be due to reversible changes in intrapulmonary tension and tend to disappear after a few weeks or months. However, in some cases they persist indefinitely. The purpose of this paper is to present a case of multiple postinfectious air cysts and to indicate the role of continuous aspiration in their treatment.

CASE REPORT

An acutely ill 10-year-old boy was admitted to the hospital in July, 1954. In 1951, he had developed measles, which was complicated by left-sided otitis media. After recovery, a foul secretion from the left ear persisted.

The present illness began in June, 1954, with high fever, rigor, cough, dyspnea, and pains in the chest. Two weeks after the onset of the illness he began to cough and to expectorate foul-smelling sputum. Upon admission he was in poor general condition, dyspneic, cyanotic, and had a fever of 40° C. Examination of the chest revealed bilateral dullness, bronchial breathing, and medium râles in the upper and lower zones. The erythrocyte sedimentation rate was 94 mm. in the first hour (Westergren) and the leukocyte count was 26,000 per cubic millimeter. X-rays of the chest showed four abscesses in the upper and lower lobes of both lungs (Fig. 1).

Staphylococcus aureus was cultured from the sputum and found to be sensitive to chloramphenicol. After treatment with chloramphenicol, the temperature subsided and the general condition improved, although expansion of the abscesses was seen on x-ray films. In August, 1954, the abscess in the left upper lobe suddenly ruptured (Fig. 2), producing a spontaneous pneumothorax. The boy was found unconscious, cyanotic, and was frothing at the mouth. The breathing was irregular and no pulse was found. Continuous intrapleural aspiration was instituted. Rapid improvement followed and after 6 days of continuous suction, roentgenograms showed disappearance of the abscess in the left upper lobe.

Two weeks later a second dramatic spontaneous pneumothorax occurred,

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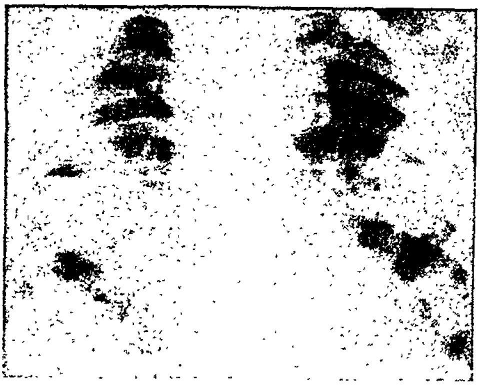
g. 1.



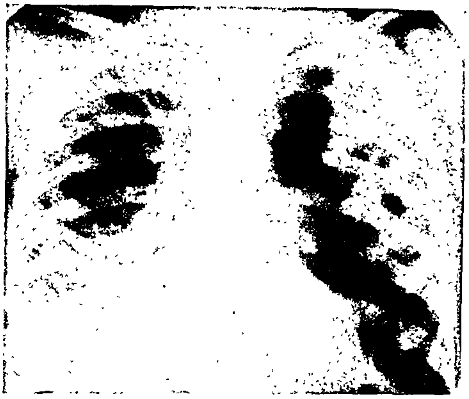
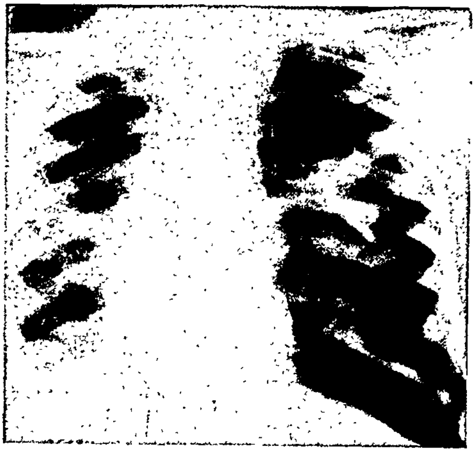


Fig.

g. 3.



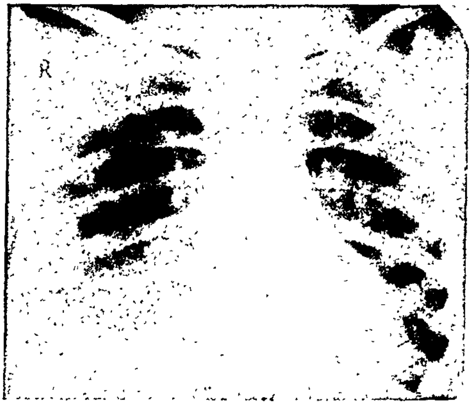
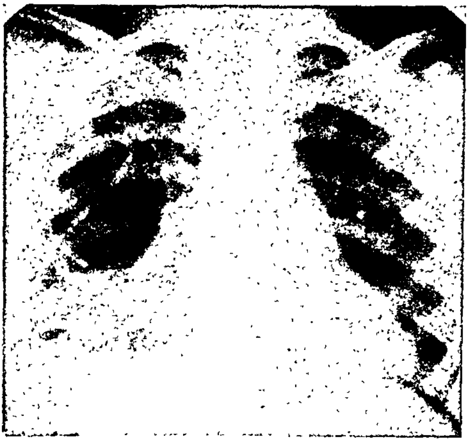


Fig. 4

g. 5.



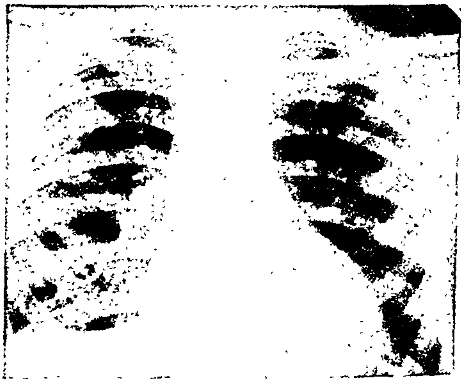


Fig. 6.

Fig. 1.—Abscesses in the left upper, left lower, right upper, and right lower lung fields.

Fig. 2.—Spontaneous pneumothorax on the left side, 2 giant tension abscesses on the right side.

Fig. 3.—Second spontaneous pneumothorax on the left. Conversion of the right abscesses into giant air cysts.

Fig. 4.—Healing of the left lung after pleural drainage. Suction drainage of the right lower air cyst.

Fig. 5.—Healing of the right lower air cyst. Suction drainage of the right upper air cyst.

Fig. 6.—Roentgenogram upon discharge shows slight fibrosis at right base.

following rupture of the abscess in the left lower lobe (Fig. 3). Again intrapleural aspiration was instituted and, after 4 days, x-ray films showed that the lung had re-expanded and that the abscess in the left lower lobe had disappeared. However, the two abscesses in the right lung occupied almost the entire volume of the right lung (Fig. 3). *Bronchoscopy showed redness of* the bronchial mucosa, particularly at the right bronchus. Attempts to deflate the cavities by bronchial suction were ineffective. In November, 1954, the temperature again rose to 40° C. Swelling developed over the left mastoid and a radical mastoidectomy was performed. The tympanic cavity and the paratympanic region were filled with granulomatous tissue. After removal of this tissue, pus under pressure was released. The lateral sinus was found to be thrombosed. The postoperative course was uneventful.

Since the giant cavities in the right lung were still found to be present after 8 months of treatment with various antibiotic drugs, transpleural drainage was decided upon. Pleural puncture revealed that over the right base the pleural cavity was obliterated. In the upper area the pleura was free in the mammary line but obliterated in the posterior axillary line. On Feb. 14, 1955, *drainage of the lower cavity* was instituted (Fig. 4). The intracavitary pressure was +4, +10 cm. of water. A multieyed catheter was inserted into the cavity and was connected with an electrical suction machine. After one week of continuous suction, the cavity disappeared completely. On Feb. 22, 1955, drainage of the upper cavity was instituted (Fig. 5). Intracavitary pressure was +6, +12 cm. of water. After 3 days of suction, this cavity also disappeared. During suction of both these cavities, a few cubic centimeters of thick, foul pus was removed. From this pus, as well as from that obtained during bronchoscopy and mastoidectomy, *Staphylococcus aureus* and *Bacillus proteus* were cultured.

The boy left the hospital in March, 1955, completely recovered. Radiograms of the chest upon discharge revealed only slight fibrosis at the right base (Fig. 6).

DISCUSSION

The annular shadows appearing during *primary staphylococcic pneumonia* or hematogeneous staphylococcic bronchopneumonia are actually giant tension abscesses. The radiographic and clinical history of our patient shows clearly the evolution from bronchopneumonic infiltrations to thick-walled, *pus-filled cavities. These later swelled* to become thin-walled balloons, due to mechanical factors, with infection now playing only a minor role. Similar formation of emphysematous bullae from miliary or cavitary staphylococcic abscesses had demonstrated in rabbits *following intravenous injection of Staphylococcus aureus.*[5] The giant air cysts constitute a special form of bullous obstructive emphysema resulting from check-valve obstruction produced by bronchial exudate and edema and later by cicatricial bronchiolar stenotic fibrosis. If they persist *indefinitely* they are frequently mistaken in later years for congenital cysts.

There are no reports dealing primarily with the treatment of these postinfectious cysts. There is, however, an extensive literature on the *treatment of emphysematous bullae* which appear mostly in cases of asthma or chronic obstructive emphysema. Head and Avery[4] successfully treated 8 patients with emphysematous bullae by Monaldi intracavitary drainage. This type of drainage has been successfully employed in the treatment of lung abscess since 1940.[10] Up to the present time, 127 cases, of which 116 recovered, have been recorded.[8] Since postinfectious air cysts are actually giant tension abscesses, Monaldi drainage is also indicated in their treatment. Expectant treatment should not exceed a period of 6 months. On the other hand, intervention may be indicated much earlier if there is marked displacement of the mediastinum or appearance of dyspnea.

The solitary giant cyst or multiple cysts located in different lobes are the only type of cysts for which Monaldi drainage is indicated. There should be a pleural bridge of adhesions at the point of intervention. Since the primary foci of suppuration are usually located peripherally, pleural reaction with subsequent obliteration of the pleural cavity is frequently present. In the absence of pleural adhesions, obliteration of pleura by poudrage is indicated.

When more than one cyst is present in a single pulmonary unit, but sufficient normal lung tissue remains, excision of the walls of the cysts and suture of the parenchyma according to the procedure of Naclerio and Langer[9] is indicated. When the postinfectious cysts have destroyed a segment or a lobe, resection of the pulmonary unit is the procedure of choice.

SUMMARY

A 10-year-old boy developed 4 hematogenous staphylococcic pulmonary abscesses following otitis media complicated by mastoiditis and thrombophlebitis of the lateral sinus. Two of the abscesses perforated and the pneumothoraces as well as the perforated abscesses were cured by continuous closed pleural drainage. The other 2 abscesses progressively inflated and were converted into giant cysts, which persisted despite 8 months of antimicrobial treatment. They healed after a few days of intracavitary aspiration. The various methods of treatment of postinfectious air cysts are discussed.

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ACCIDENTAL DIGITOXIN POISONING IN CHILDREN

Report of a Case and Review of the Literature

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INTRODUCTION

ACCIDENTAL drug poisoning in children is common and is being seen more frequently each year. Digitalis intoxication is common also and is increasing, paralleling the increasing number of older people and hence the number of patients requiring treatment with digitalis. Accidental digitalis poisoning is rare, especially in children, as evidenced by the scarcity of material in the literature on this subject. However, small children have an unquenchable curiosity, which causes them particularly to put things in their mouths. It is thus a grave danger for older people to leave digitalis within the reach of small children in the house.

Bergy and associates[1] reported a case of overwhelming acute digitoxin poisoning in an adult. They surveyed the world literature and found seven other cases of accidental digitalis poisoning. However, none of these was a child. A further search of the English medical literature revealed two case reports of accidental digitalis poisoning in children. Both of these cases occurred in the British Isles.

Allen[2] reported a case of a 3-year-old child who swallowed 1.2 mg. of Digitaline Nativelle. After six hours the child began to vomit. On the second day after the ingestion he had a pulse rate as low as 52 per minute. He was treated with atropine and strychnine and on the fourth day apparently had recovered completely.

The second case was reported by Soderberg.[3] The patient was a 2-year-old child who swallowed 33 tablets of folium digitalis (0.05 Gm. each) totaling 1.65 Gm. Gastric lavage was unsuccessful but the child began to vomit in three hours. On the following day, the electrocardiogram showed first degree A-V block (P-R interval, 0.24-0.26 seconds) and a temporary complete A-V block with a varying rate of about 80 per minute. The patient was well clinically on the third day but the electrocardiogram did not return to normal until one month after ingestion of the digitalis.

Recently I observed accidental digitoxin poisoning in a child. In view of its rarity, it was thought to be of considerable interest and worth reporting.

CASE REPORT

A 2-year-old white boy (W. C. G. H. Case #73279) was first seen in the emergency room at 1:00 P.M. on Dec. 20, 1956. Apparently the child had been in his usual good health until noon on the day of admission, at which time he began to retch and vomit. He became seriously ill quite rapidly and vomited many times. It was not until shortly before admission that the grandmother's bottle of digitoxin was found empty. The family thought the child had taken from 12 to 15 tablets of digitoxin (0.1 mg. size). The child apparently took the digitoxin shortly after 8:00 A.M. on the day of admission. When examined in the emergency room, he was lethargic, vomited repeatedly, and appeared acutely ill. The heart rate was 96 and the rhythm was somewhat irregular. A Grade 2 systolic murmur was heard in the second and third intercostal spaces on the left. The remainder of the physical findings were normal. The child weighed 30 pounds.

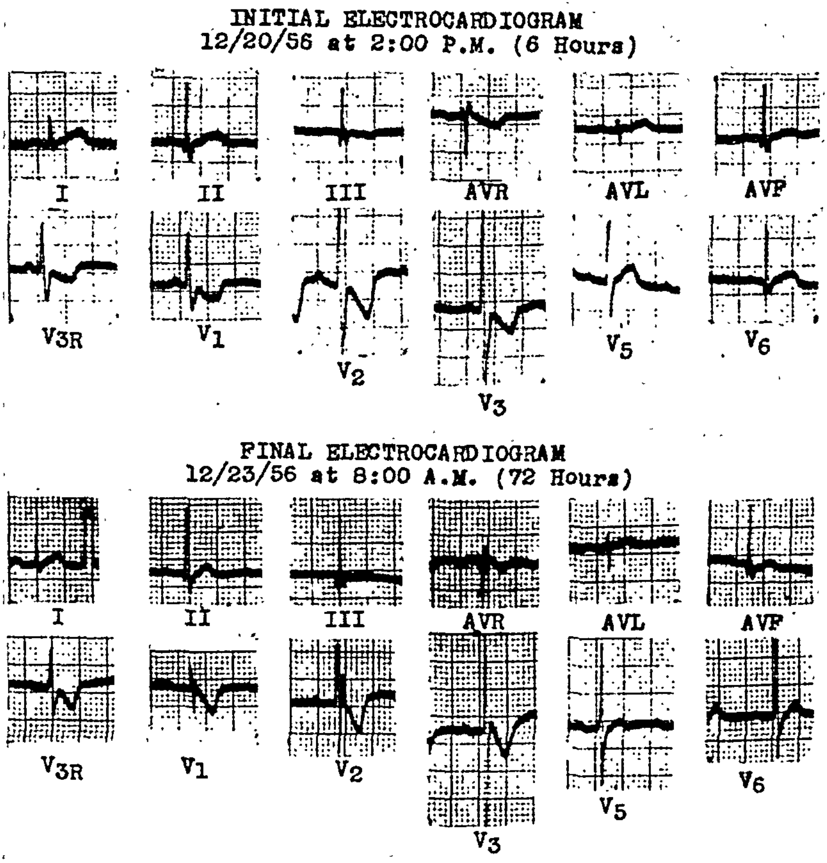
INITIAL ELECTROCARDIOGRAM
12/20/56 at 2:00 P.M. (6 Hours)
I
II
III
AVR
AVL
AVF
V3R
V1
V2
V3
V5
V6
FINAL ELECTROCARDIOGRAM
12/23/56 at 8:00 A.M. (72 Hours)
I
II
III
AVR
AVL
AVF
V3R
V1
V2
V3
V5
V6

Fig. 1.—The initial and final electrocardiograms are shown here for comparison.

Laboratory studies showed the following: hemoglobin, 13.9 Gm.; red blood count, 5.1 million; white blood count, 11,250, 85 per cent neutrophils, 12 per cent lymphocytes, 3 per cent monocytes. Urinalysis showed specific gravity, 1.020; acetone, strongly positive; occasional hyaline cast.

After a gastric lavage, the patient was admitted to the pediatric ward where the initial electrocardiogram was taken (Fig. 1). An attempt to give potassium chloride was unsuccessful because the child was vomiting and was unable to retain oral fluids or medication. He continued to be lethargic and irritable and the pulse revealed "dropped beats." After an electrocardiogram was taken at 7:00 P.M., intravenous fluids consisting of 500 c.c.

of 5 per cent dextrose in water with 10 mEq (750 mg.) of potassium chloride were started at 20 drops per minute. In 3 hours the pulse was less irregular. Occasional twitching of the skeletal muscles was noted about midnight. Repeated attempts to sip water were followed by emesis. At 10:00 A.M. the next day the initial intravenous therapy was followed by 250 c.c. of 2.5 per cent dextrose in half-strength lactated Ringer's solution (39 mg. of potassium chloride). He was still lethargic but responded when aroused. Because of vomiting, an injection of Thorazine (5 mg.) was given at 3 P.M. and another at 8:30 P.M. (Dec. 21, 1956) with fair results. The patient

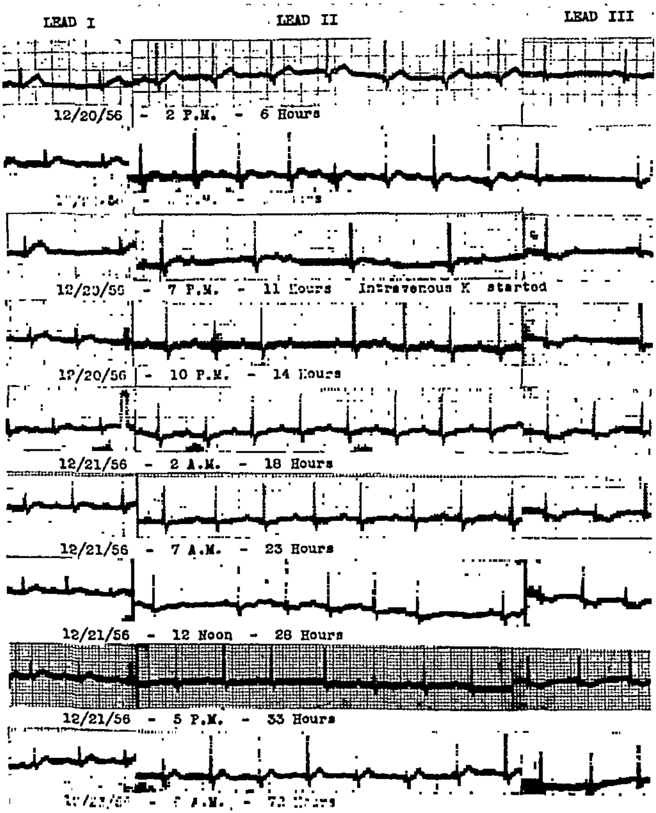
LEAD I
LEAD II
LEAD III
12/20/56 - 2 P.M. - 6 Hours
12/20/56 - 7 P.M. - 11 Hours Intravenous K started
12/20/56 - 10 P.M. - 14 Hours
12/21/56 - 2 A.M. - 18 Hours
12/21/56 - 7 A.M. - 23 Hours
12/21/56 - 12 Noon - 28 Hours
12/21/56 - 5 P.M. - 33 Hours
12/23/56 - 7 A.M. - 72 Hours

Fig. 2.—Serial electrocardiograms on patient.

was now voiding well and the intravenous infusion was continued with 250 c.c. of 5 per cent dextrose in 0.45 per cent saline. During the evening of the second hospital day, he became much more alert but did not retain oral fluids well until late that evening. He was then given oral potassium chloride, 125 mg. every 4 hours. Two days later the child was alert, eating and drinking satisfactorily, and appeared well. No residual signs or symptoms were noted. The child was dismissed. One week later the patient's physician reported that there were no further symptoms or findings.

TABLE I. DATA FROM SERIAL ELECTROCARDIOGRAMS ON PATIENT (FIG. 2)

HOURS AFTER INGESTION	P-R* INTERVAL (SEC.)	Q-T† INTERVAL (SEC.)	ATRIAL RATE	VENT. RATE	COMMENT
6	0.14	0.28	88	88	Normal sinus rhythm
9	0.23	0.24	107	107	First degree A-V block, rare dropped beat
11	0.18–0.23	0.28	107	54	Second degree A-V block
14	0.25	0.24	103	90	First degree A-V block, occasional dropped beat
18	0.24	0.24	107	107	First degree A-V block
23	0.24	0.24	103	103	First degree A-V block
28	0.19	0.24	109	90	First degree A-V block, occasional dropped beat
33	0.18	0.24	100	100	First degree A-V block
72	0.16	0.24	100	100	Normal sinus rhythm

*Upper limits of normal for 2-year-old child at rate of 90-110 is 0.16 second.

†Lower limits of normal for 2-year-old child at rate of 88 is 0.28 second; at 100 is 0.27 second; at 109 is 0.26 second.

DISCUSSION

In the otherwise healthy laboratory animal,[4, 5] the first toxic manifestations of digitalis poisoning are strong vagal stimulation. They consist of bradycardia, cardiac irregularities, diastolic pauses, and an idioventricular rhythm. This may or may not be followed by increasing muscular irritability resulting in an increase in the ventricular rate, the ventricles functioning independently of the atria. As the toxicity increases, the heart progresses into ventricular fibrillation and death follows. In animals so poisoned, microscopic examination of the heart shows focal areas of necrosis, especially *in the subendocardium and in the posterior* papillary muscles of the left ventricle. These lesions are more common in older animals and in the presence of experimentally induced hyperthyroidism.

Although digitalis poisoning in man may be manifested by the same variety of rhythmic disorders seen in animals, similar pathologic lesions have not been demonstrated. It is well known that digitalis has been responsible for almost every known type of arrhythmia and conduction disorder.[4, 6, 7]

The symptoms of digitalis intoxication usually begin with anorexia, nausea, and vomiting.[4, 6, 7, 8, 9, 10] Occasionally there may be diarrhea, salivation, abdominal discomfort, substernal pain, and rarely a hemorrhagic gastritis. Respirations may be normal or the patient may become dyspneic. Many patients suffer fatigue and become drowsy. A few lose consciousness. Others become restless, irritable, disoriented, and rarely they may have hallucinations and delirium. Some develop headaches, tremors, myalgias, arthralgias, and sometimes convulsions. Although it is rare, psychoses may be observed as a late effect. Disturbances in color vision are common and often these patients are unable to focus their eyes properly; others may have diplopia, amblyopia, and scotomata. Occasionally, there are vestibular disturbances and impairment of renal function.

The electrocardiogram[4, 6, 7] first shows flattening of the T wave which later becomes inverted. The usual digitalis ST segment is noted. As toxicity increases, the P-R interval is prolonged and the Q-T interval is diminished. The electrocardiogram shows changes in rhythm and conduction as described.

The patient under discussion demonstrated many of these signs and symptoms. Many of the subjective symptoms may have been missed because of his age. The serial electrocardiograms (Fig. 2) demonstrate well the progression of the toxic effects to one of the most common of the conduction defects.

The toxic dose of digitoxin is difficult to estimate because of the many variables and individual differences. Master[11] states that the initial therapeutic digitalization dose is about 50 to 60 per cent of the toxic dose. Nadas,[12] in a study of the use of digitoxin in 41 children with various cardiac diseases, noted that none of the patients showed a satisfactory response with less than the "average" adult digitalizing dose of 0.01 mg. per pound of body weight. There were also no satisfactory responses in patients requiring more than 0.03 mg. per pound. The majority of their patients showing digitoxin toxicity received dosages of 0.015 mg. per pound of body weight. Considering further that children, in general, require 50 per cent more digitoxin per unit of body weight than adults,[12-14] we would calculate the average digitalizing dose as 0.015 mg. per pound of body weight (using 0.01 mg. per pound as average for adults). Using Master's figures, the average toxic dose for children would be 0.025 to 0.03 mg. per pound of body weight. If we apply these figures to our patient, whose weight was 30 pounds, the estimated toxic dose of digitoxin would be 0.75 to 0.90 mg. The patient received 1.2 to 1.5 mg. of digitoxin, which is well in excess of this estimated toxic dose.

The present treatment[4, 6] of digitalis poisoning is chiefly supportive and symptomatic. Cessation of intake of the drug and promotion of its excretion are desirable. Pronestyl[4, 6, 15] and quinidine[4, 6, 16] have been used to counteract and reverse the arrhythmias. However, the danger of the use of digitalis and quinidine simultaneously has been pointed out by Gold.[16] It would be more desirable to have an agent to use before the onset of the arrhythmia. Numerous workers[17, 18] have used a 10 per cent solution of magnesium sulfate intravenously to correct the arrhythmias induced by digitalis. The disadvantages of the use of magnesium sulfate are its transient action and the occasional tendency to increase the basic arrhythmia.[4] There have been several investigations[4, 6, 19, 20] concerning the use of potassium in digitalis intoxication. Numerous workers have abolished various arrhythmias with potassium; about half succeeded when the arrhythmias were not due to digitalis and almost all succeeded when they were due to digitalis.

It has been demonstrated that there is a depletion of potassium in the myocardium in digitalis intoxication. Also, myocardial potassium depletion is observed in states of anoxia, myocardial failure, myocardial infarction, following diuresis, diabetic acidosis, metabolic alkalosis, and intestinal disorders.[20-24] In these conditions there is increased sensitivity to digitalis. In the isolated heart preparation the effect of digitalis can be enhanced or inhibited by appropriate variation of the potassium ion concentration in the perfusate.[25] It has been suggested that potassium might inhibit the cardiac effects of digitalis by depressing cardiac irritability and also by offsetting the specific loss of potassium from the heart that occurs when it is exposed to large or toxic amounts of digitalis.[4, 6, 23, 24]

The series of electrocardiographic tracings on this patient demonstrates the progression of the electrocardiographic signs of digitalis poisoning until the administration of the intravenous fluids containing potassium. After the beginning of this therapy, there was a progressive decrease in the signs of digitalis intoxication. This reversal of the progression of these signs occurred earlier than would be expected considering the peak of the effect and the length of action of digitoxin. Most reports[4, 6] on the treatment of digitalis intoxication have concluded that potassium is relatively nontoxic in the presence of normal renal function. Admittedly, the use of intravenous potassium-containing fluids is attended with more danger than oral medication, but the persistent vomiting made the intravenous route a necessity. The fluids did not contain a large amount of potassium and they were administered slowly. The use of an intravenous infusion not only afforded a vehicle in which to administer potassium ions, but it also helped to correct the fluid loss and electrolyte imbalance from the severe vomiting and cessation of fluid intake. It further helped to correct the acidosis of dehydration which itself may cause potassium loss; and it helped keep up an adequate urine volume to promote excretion of digitoxin and any excess of potassium which had been administered.

SUMMARY AND CONCLUSIONS

Although accidental drug poisoning in children is common, accidental digitalis poisoning in children is rare as evidenced by the scarcity of material in the literature on this subject. Two case reports of accidental digitalis poisoning from the British Isles are cited. These resemble our case in both the amount ingested and the course of events following the ingestion.

The patient reported here was a 2-year-old boy who ate about 1.5 mg. of digitoxin. He displayed a number of the signs and symptoms of digitalis intoxication. Serial electrocardiograms showed a progression of the electrocardiographic manifestations of digitalis toxicity which continued until the initiation of intravenous fluids containing potassium. After this there was a gradual decrease in the electrocardiographic manifestations of toxicity returning to a normal electrocardiogram three days after ingestion of the digitoxin.

The toxic effects of digitalis are discussed briefly as well as the treatment of digitalis intoxication. Although no definite conclusion can be made concerning the effect of potassium therapy, it appeared to have had a beneficial effect on this patient, at least on the electrocardiographic signs of digitalis toxicity.

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NARCOTIC WITHDRAWAL SYMPTOMS IN THE NEWBORN INFANT RESULTING FROM MATERNAL ADDICTION

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DURING the past decade, narcotic addiction has received increasing attention in both lay and medical publications However, the adverse effects of maternal addiction on the newborn baby has received scant mention. It would seem appropriate at this time to stimulate an awareness of this problem because of the necessity of early appropriate treatment in the more severely addicted infants.

Murray[1] described 18 infants delivered at Sydenham Hospital in New York City during 1953, 1954, and the first ten months of 1955, born of mothers all of whom were acknowledged heroin addicts. He found that heroin addiction in the mother is frequently associated with prematurity in the baby. Fifteen babies developed withdrawal symptoms within 1 to 56 hours after birth and 4 died, a mortality of approximately 25 per cent. In addition to characteristic withdrawal symptoms such as tremors, vomiting, diarrhea, cyanosis, anorexia, and inanition, these babies developed respiratory symptoms consisting of increased production of mucus. The amount of mucus was great enough to interfere with respiration, requiring aspiration and oxygen. The babies who succumbed apparently died of respiratory failure.

Five babies were treated for their withdrawal symptoms with methadone given in doses of 0.5 mg. to 1 mg. every four to twelve hours and continued in decreasing doses for several days or weeks. All of these babies survived and appeared to do better than those on standard therapy with paregoric or barbiturates.

Goodfriend and associates[2] reviewed the literature and reported 10 additional cases in 1956. They stressed the importance of making the diagnosis early so that effective therapy could be instituted without delay. It was found that the over-all reported mortality in infants varied from approximately 34 to 93 per cent, depending upon whether or not therapy was given. It is interesting to note that in 2 of their cases the presence of hepatitis in the mother presented the clue to the history of addiction. Serum hepatitis occurs frequently in addicts because of common usage of contaminated needles and syringes.

During the same year, Slobody and his associates[3] presented a series of 22 newborn infants born of addicted mothers over a period of five years. Eighteen of these women were heroin addicts and their individual daily doses varied from 2 mg. to 45 mg. Nine or almost half of the babies were premature by weight, i.e., less than 2,500 grams. The symptoms were

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similar to the ones described by previous authors (Table I). They found a direct relationship between the severity of the infant's signs and symptoms and the size of the maternal narcotic dosage. Recovery took place in all the babies.

TABLE I. NARCOTIC WITHDRAWAL SIGNS AND SYMPTOMS IN THE NEWBORN INFANT

Restlessness and irritability
Tremors
Convulsions
Fever
Yawning
Vomiting
Diarrhea
Anorexia
Inanition
Sneezing
Intermittent cyanosis
Respiratory difficulty associated with increased mucus
Excessive high-pitched crying
Diaphoresis

No treatment was necessary in 9 cases because of the mild course. In the remaining 13, treatment included drugs such as paregoric, Thorazine, phenobarbital, and reserpine. Of these the most effective were Thorazine and paregoric. Since psychic dependence to narcotics does not exist in newborns they were much easier to cure. However, the authors advise that the most appropriate solution is removal from the mother.

Steg[4] reported 3 infants seen at the Boston City Hospital during a period of fourteen months, all of whom survived without definitive treatment. The symptoms in these babies paralleled those reported previously. She stresses the importance of the cry in these infants describing it as "louder, higher-pitched, and more continuous than the cry ordinarily observed in infants with organic disturbance of the central nervous system."

Recently, the first case of a baby born to an admitted heroin addict occurred in our hospital, the details of which follow.

CASE REPORT

Baby S. was delivered of a white 24-year-old woman who arrived at the hospital in labor. She had not had any prenatal care. Shortly after delivery, numerous needle puncture marks were noted on both her arms and forearms and, upon questioning, the mother freely admitted to being a heroin addict. She proved to be extremely uncooperative other than giving this information and disappeared from the hospital on the following day. Although she was given no Demerol and the delivery was a simple spontaneous one, the baby appeared unduly narcotized. It is quite likely that the mother had had a recent dose of heroin shortly before her arrival at the hospital. The baby's birth weight was 5 pounds, 14 ounces.

Toward the end of the first twenty-four hours the baby became very restless and irritable and developed tremors and twitchings. The classical features of tetany such as the Chvostek, Trousseau, and peroneal signs, and carpopedal spasm were absent. An initial blood calcium specimen was lost but a repeat one was normal. Calcium gluconate was given with no apparent relief. Shortly thereafter, vomiting and diarrhea occurred accompanied by constant shrill, high-pitched crying and refusal to take feedings. As a result of the restlessness, severe excoriation of the heels and knees occurred. Accompanying these symptons were a persistent nasal stuffiness, increased sweating, severe enough to produce a rash and a rise in temperature to slightly over 100° F., rectally. There were several bouts of intermittent cyanosis within the first forty-eight hours. All the symptoms subsided gradually over a period of a week to ten days at which time the infant began to thrive, taking her formula eagerly and gaining weight. She was discharged to a welfare agency at approximately 5 weeks of age, weighing 6 pounds, 9 ounces and free of all symptoms.

Since the Pediatric Service was not aware of the mother's addiction for a few days, it was decided to withhold treatment. The infant recovered without definitive therapy although the symptoms were characteristic enough to suggest earlier inquiry about the mother. Had this been done soon after delivery the baby would undoubtedly have received medication.

DISCUSSION

It is quite possible that many cases of narcotic addiction in newborn infants have been overlooked. Since there has been an increase in drug traffic during the past decade there may well be a rise in the number of addicted mothers. Because the mortality of untreated babies is high it is important that pediatricians as well as obstetricians be aware of the withdrawal signs and symptoms in newborns so that appropriate therapy can be instituted early whenever necessary. These babies are usually irritable and restless. They cry continuously with a shrill, piercing scream. Feedings are taken poorly and are associated with frequent vomiting and diarrhea, resulting in inanition. Twitchings, tremors, and even frank convulsive seizures occur accompanied by intermittent cyanosis. This might lead one to suspect tetany or central nervous system injury. In addition, the infants present withdrawal symptoms found in adults such as yawning, nasal stuffiness, sneezing, increased sweating, and fever.

Whether the infant will develop symptoms depends to a large extent upon the time the mother had her last dose of narcotics. As Goodfriend[3] and Steg[4] have noted, if the mother has had treatment for several weeks prior to delivery, the chances of the baby having clinical signs and symptoms will be slight whereas if the parent has taken narcotics until the end of pregnancy the infant will probably show the characteristic picture of addiction.

Treatment consists in administering opiates or tranquilizers in gradually diminishing amounts over a period of days to weeks. Although paregoric and barbituates have been used by most authors, others have found Thorazine and reserpine effective. Since infants of addicted mothers are rarely nursed these days, the question of adequate secretion of narcotics in breast milk sufficient to maintain the baby free of symptoms[5, 6] is more academic than real. Furthermore, the increased emotional attachment of an addicted nursing mother toward her newborn infant would further complicate the problem of separating the child from the parent.

Although it has been implied that these infants are apparently cured completely once their symptoms have subsided it would appear that a prolonged follow-up period is in order. If some of these babies are ill enough to have severe respiratory symptoms, cyanosis, and convulsive seizures, it may be reasonable to assume that a fraction of them could be left with some residual organic brain damage. To my knowledge there are no data in the current literature dealing with this aspect of the problem.

Since many, if not most, of these babies are placed for adoption, one may ponder the question whether these infants are a good adoptive risk. Could the mother's emotional instability which led her to resort to narcotics foreshadow the neuro-hereditary pattern of her offspring—or is the infant's ultimate emotional development primarily one of environment? At any rate, the sociological and genetic aspects of the problem assume increasing importance.

SUMMARY AND CONCLUSION

During the past decade there has been a rise in narcotic addiction. This has received increasing attention in the lay press and in scientific publications. However, there has been little mentioned of the adverse effects of maternal addiction on the newborn baby.

Abstinence signs and symptoms in these infants present a fairly characteristic picture which is not difficult to diagnose provided it is kept in mind.

The mortality in untreated infants manifesting withdrawal symptoms is high. Early diagnosis is therefore very important.

Treatment consists in administering decreasing doses of opiates, barbiturates, Thorazine, or reserpine over a period of days or weeks.

Since newborn addiction is not on a psychological basis, cure is much easier to accomplish. However, to ensure this, removal of these babies from the environment of the mother is important.

A prolonged follow-up study is suggested to determine whether any residual effects and/or organic damage from narcotic drug addiction have remained in these babies. Equally important is the evaluation of their emotional development.

The problem is not only medical but poses important genetic and social considerations. It seems appropriate at this time to bring further awareness of this to all physicians caring for the newborn infant.

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Clinical Pathological Conference

THE CHILDREN'S MEDICAL CENTER
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SIDNEY FARBER, EDITOR
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CLINICAL HISTORY

THIS boy was well, save for an episode of cyanosis on the first day of life, until the age of 8 months, when he developed an upper respiratory infection with fever, cough, and wheezing. This infection lasted several days and responded to antibiotic therapy. A heart murmur was first heard at the time of this illness. At the age of 14 months he began to have tantrums, associated with episodes of cyanosis, and stiffening of several minutes' duration. From this time it was noted that he developed slight cyanosis during upper respiratory infections.

He was first admitted to The Children's Medical Center at 18 months of age because of rapid and difficult respirations. Physical examination then revealed a poorly nourished boy, below the third percentile for height and weight. The temperature was 100° F. (rectal), the pulse rate was 120 per minute, and the respiratory rate 55 per minute. The blood pressure was 150 mm. Hg systolic and 80 mm. Hg diastolic in both arms. A blood pressure of 45 mm. Hg by the flush method was obtained in the legs. The femoral pulses were weak. The chest was emphysematous, with a left-sided prominence. Râles, rhonchi, and wheezes were heard throughout both lung fields on auscultation. The heart was slightly enlarged to the left. A questionable murmur and a third heart sound were heard, loudest at the apex. There were grade II mid-diastolic and grade III systolic murmurs at the apex; the latter was transmitted to the back and axilla. A grade II systolic murmur with a faintly heard diastolic component was noted at the second left interspace and was transmitted to the cervical region. The liver was palpable 3.0 cm. below the right costal margin.

The admission laboratory data were: hemoglobin 10.5 Gm. per cent, leukocytes normal in number and differential count. The electrocardiogram was interpreted as showing auricular hypertrophy, "P-mitrale," and an incomplete right bundle branch block with right ventricular hypertrophy that was unduly marked for the age of the child. The left ventricular electrical potentials suggested combined ventricular hypertrophy. The chest roentgenograms revealed a globular heart and bilateral ventricular enlargement, the right ventricle being more enlarged than the left. There was a concavity in the region of the main pulmonary artery with a narrow superior mediastinum. The right auricle appeared enlarged. The aorta lay on the left. The pulmonary vasculature was increased, probably on the basis of active and passive congestion.

The child was treated for bronchitis and congestive failure, with improvement. He was discharged home on Digoxin and prophylactic Gantrisin.

At age 21 months, he was again admitted with a recurrence of his fever, cough, and respiratory difficulty. A thrill was now palpated in the suprasternal notch and a grade II continuous murmur was heard below the left clavicle. The liver was 6.0 cm. and the spleen 3.0 cm. below the costal margin. No other changes in the physical examination or laboratory findings were noted. With antibiotics and Mercuhydrin, he improved and was discharged after 2 weeks of hospitalization on his previous maintenance therapy.

TABLE I. CARDIAC CATHETERIZATION DATA

POSITION OF CATHETER	OXYGEN CONTENT VOLUME PER CENT	OXYGEN CAPACITY VOLUME PER CENT	OXYGEN SATURATION PER CENT	PRESSURES MM. HG AT 25 MONTHS	PRESSURES MM. HG AT 34 MONTHS
Right auricle	11.55			4	3
Right mid-ventricle	11.70			75*/ 2†/13‡	47*/ 0†/17‡
Right pulmonary artery	11.70			70*/30†	37*/10†
Pulmonary capillary	15.40			13	12
Left axillary artery	15.25	15.4	99	150/75	120/66
Left femoral artery	15.25		99	88/56	85/62

*Systolic.
†Minimal diastolic.
‡End diastolic.

There were five admissions to a hospital in another state over the next year, for the same complaints. A cardiac catheterization was done at age 25 months (the results are listed in Table I).

His final admission took place at 34 months of age, after a further recurrence of similar symptoms. Now, the physical examination revealed a temperature of 98° F., respirations 32 per minute, pulse 100 per minute, blood pressure 150 mm. Hg systolic and 70 mm. Hg diastolic in the right arm, and 180 systolic and 30 diastolic in the left arm. The blood pressure was not obtained in the legs. He appeared ill and in acute respiratory distress. The chest was barrel shaped with subcostal retraction. The lung fields were hyperresonant; râles, rhonchi, and wheezes were heard throughout. The pulmonic second sound was increased, the other murmurs remaining as before. The liver and spleen were still enlarged.

Laboratory tests gave the following data: the urine was normal, the old tuberculin test negative, the blood hemoglobin level was 12.5 Gm. per cent, and erythrocytes 4.19 million per cubic millimeter. The hematocrit was 35 per cent. The leukocytes numbered 19.6 thousand with 72 per cent polymorphonuclears and 28 per cent lymphocytes on the smear. The serum globulin level was 4.7 Gm. per cent. An estimation of the concentration of sweat electrolytes was within normal values. The chest roentgenograms revealed mottled confluent densities in both lung fields, but more prominently on the right. This was interpreted to represent chronic congestion with a superimposed infection.

Vigorous antispasmodic and antibiotic therapy was begun, and prompt clinical improvement occurred so that digitalis was discontinued, although râles and rhonchi were present in the lung. Skin tests showed him to be sensitive to a large number of antigens. A month after entry, digitalis and Mercuhydrin were administered again but without effect on the pulmonary findings or body weight. Adrenalin and cortisone were also tried for 3 days, with no effect. A repeat cardiac catheterization was performed and, ten days later, an operation was done, during the course of which he died.

DISCUSSION

DR. ALLAN L. FRIEDLICH.*—The patient had repeated severe respiratory infections with fever, cough, and wheezing, which responded to antibiotics. This profusion of respiratory infections always brings to mind, in a patient with congenital heart disease, a left-to-right shunt with an increased pulmonary blood flow. This seems to have a peculiar ability to make children more susceptible to respiratory infections. The temper tantrums, associated with slight cyanosis and stiffening for several minutes' duration, suggest spells seen in tetralogy of Fallot and tricuspid atresia, but since no further mention is made of this, I think we can omit any further consideration of it.

The blood pressure in the arms, on the first admission here, was 150/80, which I don't have to remind you is a considerable hypertension for a child of this age, although in an adult it would not be particularly alarming.

While there was hypertension in the arms, the blood pressure could not be auscultated in the legs; therefore, a flush pressure determination was done instead. This was found to be 45 mm. Hg and approximates, I am told, the mean arterial pressure in the legs, so there was a distinct pressure gradient between the arms and the legs. The femoral pulses were poorly felt. Therefore, there is certainly no question that a coarctation of the aorta was present.

The split second heart sound again calls to mind the possibility of the presence of an atrial septal defect, of which a split second sound is rather characteristic. The prominent apical third sound I interpret as a gallop, if the grade III systolic murmur which was transmitted to the back and axilla was maximal at the apex. The systolic murmur in the second left interspace is in keeping with the diagnosis of coarctation; it may extend into diastole and thus simulate a continuous murmur due to diastolic flow through the coarctation. In the presence of continuous murmur, a patent ductus arteriosus, or a so-called "pseudotruncus arteriosus," with extensive collateral circulation in the lungs must be considered. X-ray findings will rule out the latter diagnosis entirely. The grade II mid-diastolic rumble heard at the apex can be due to mitral valve dicease; dilation of the ventricle resulting in relative mitral stenosis, as one sees in children severely ill with acute rheumatic cardititis, or to a condition associated with a large pulmonary blood flow.

The electrocardiographic changes of left auricular hypertrophy focus our attention on lesions on the left side of the heart, principally coarctation or mitral stenosis. The electrocardiographic evidence of incomplete right bundle branch block and right ventricular hypertrophy, the split second sound, and the tendency toward repeated pulmonary infections all suggest the possibility of an atrial septal defect.

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May we see the x-rays?

DR. MARTIN H. WITTENBORG.—The fluoroscopy revealed that the heart was enlarged to the right and the left, the atria participating in the enlargement, but Dr. Currarino felt that the right ventricular enlargement was predominant. The region where the pulmonary artery normally lies was diminished in width at all times, suggesting that the main pulmonary artery segment was either small, absent, or malposed. Since he could not find it any where else, he assumed that it was certainly either absent or hypoplastic.

DR. FRIEDLICH.—Do you think, knowing this child's clinical findings indicating coarctation of the aorta, that the appearance of a narrow waist could be produced by a small aortic knob?

DR. WITTENBORG.—In general, in coarctation, even in the presence of a hypoplastic aorta, little confusion with the pulmonary artery occurs in interpretation of the radiologic evidence. In this examination we can be sure that the pulmonary artery is not large and is probably hypoplastic. The aorta definitely lies on the left, and the ascending aorta is small. There is evidence to suggest a descending aorta on the left, but no signs to suggest a coarctation. We cannot usually visualize the coarcted segment on a routine chest film but must rely on signs of collateral circulation or post-stenotic dilatation in conjunction with the changes in heart contours. The findings here are not characteristic of an uncomplicated coarctation.

DR. FRIEDLICH.—Do you think the pulmonary blood flow is increased?

DR. WITTENBORG.—The pulmonary blood flow is hard to evaluate in this particular patient because of inflammatory changes, but it is not grossly altered.

DR. FRIEDLICH.—Do you see any cysts in the lungs?

DR. WITTENBORG.—There are inflammatory changes in the right lower lobe, mixed atelectasis and hyperaeration, but no true pulmonary cysts. In the last film taken, the inflammatory lesions have cleared.

DR. FRIEDLICH.—We have, then, both radiologic and electrocardiographic evidence of right ventricular hypertrophy, and that is going to be hard to explain.

What can we say about the catheterization data? First, we have confirmation of the clinical observation of hypertension in the upper part of the body and hypotension in the lower, with pressures in the axillary artery of 150/75, and in the left femoral artery of 88/56. It may be unwise to use the left axillary artery rather than the right because, of course, sometimes the left subclavian arery may be involved in the coarcted segment and one may not get a true value for the pressure gradient. The pulmonary capillary pressure was 13 mm. Hg, which is distinctly elevated. This means that there is some interference with the function of the left ventricle, either by left ventricular constriction of endocardial, pericardial, or myocardial origin, or by mitral stenosis or regurgitation. One cannot differentiate which of these possibilities is responsible. The pulmonary artery pressure was 70/30, which is moderately elevated. This may be secondary to primary lung disease, to a left-to-right shunt, or to mitral stenosis. In the latter instance, the obstruction in the pulmonary arterioles may be even more important than that of the mitral valve. Since the right ventricular pressure was 75 mm. Hg systolic and that in the pulmonary artery was 70, I think we can exclude significant pulmonary stenosis. The right ventricular end diastolic pressure was 13, when the right atrial pressure was only 4, and it would be interesting also to know whether the configuration of the right ventricular pressure tracing showed any suggestion of a diastolic plateau which would suggest constriction of the right ventricle, either pericardially or endocardially.

At the last admission, the blood pressure in the right arm was 150/70, and in the left arm 180/30. Now, what do such differences mean? It is hard to do exact comparisons in pressure in the two arms, unless they can be done simultaneously. I doubt that it means an anomalous right subclavian artery arising from the aorta, below a coarctation, because the blood pressure was not obtainable in the leg—although I am always worried about what would happen if there was a coarctation involving the left subclavian.

The presence of a high normal level of gamma globulin and the normal sweat test effectively rule out agammaglobulinemia and mucoviscidosis as causes for the repeated respiratory infections. The confluent densities in the x-ray responded very quickly to a regime of antibiotics, which rules out pulmonary infarction or bizarre infections as their cause.

The child, by skin test, was allergic to a large number of antigens. This was very obviously a sick child and one who did not seem to be a good risk for surgery for coarctation. The inability to see the area of coarctation, and the possibility of other associated lesions, might very well have suggested the possibility of doing an angiocardiogram to clarify the anatomy of the situation before operation, and I would assume that the child's critical condition and also the multiple sensitivities were reasons why an angiocardiogram was not done in a patient in whom the presence of associated lesions were suspected but not established.

At the second catheter study, the oxygen content in the superior vena cava was the same as that in the right auricle, right ventricle, and pulmonary artery, ruling out any significant left-to-right shunt in the heart or into the pulmonary artery. Is there a right-to-left shunt? No, because the arterial oxygen samples were 99 per cent saturated. Is there any shunt through a patent ductus arteriosus from the pulmonary artery into the aorta, perhaps below the coarctation? Here, too, the answer is "No," because the oxygen content of the femoral arterial blood is the same as that in the axillary artery. The pressure measurements again indicate a high pulmonary capillary pressure but with less pulmonary hypertension.

I am sure that operation performed was for coarctation of the aorta. It was undoubtedly realized that the risk in this child was very high. The results of surgery in this age group are disappointing from the standpoint of the high risk, with mortality rates of 50 to 75 per cent. The cardiac group at this hospital has made a considerable contribution by pointing out the favorable results of medical treatment of infants with coarctation who are in congestive failure. Yet, if one uses optimal medical treatment and the child is still in difficulty, operation must be seriously considered.

If this child had mitral regurgitation, the volume of mitral regurgitation would be partially dependent on the systolic pressure developed in the left ventricle. It might reasonably be hoped that by removing an aortic block and lowering the systolic pressure, the volume of mitral regurgitation would be decreased and an additional relief obtained. From the auscultatory findings and catheter data, I would think that this lesion probably involved the mitral valve. Mitral regurgitation of this sort, as an isolated defect, is rare, but can occur as duplication of the mitral orifice or fenestration of the valve. More commonly, congenital mitral regurgitation would be associated with endocardial sclerosis. Other commonly associated defects seen in coarctation are bicuspid aortic valve and atrial and ventricular defects. There is a good deal to suggest, in this case, that the lungs may have been giving him more trouble than his heart. Dr. Beecher and others have pointed out the hazards of high accumulations of carbon dioxide during thoracotomies, even with normal lungs. With pulmonary insufficiency, this would be an even greater hazard in an operation in which one lung has to be collapsed in order to get adequate exposure. I am sure that every effort was made to ventilate this child well during the operation. The underlying cause of the pulmonary difficulty here is rather hard to determine. Mucoviscidosis and agammaglobulinemia have been pretty well ruled out. A left-to-right shunt was ruled out by the catheterization studies. There is no indication of a vascular ring or other causes of respiratory tract obstruction by x-ray and no known aspiration. I suppose we would have to feel that this child has a bronchiolectasis or bronchiectasis with compensatory areas of emphysema, repeated respiratory infections, and pulmonary insufficiency on these grounds.

In summary, then, my diagnoses include coarctation of the aorta, mitral valve involvement due to subendocardial sclerosis, congestive failure, and bronchiolectasis or bronchiectasis.

DR. GUSTAVE E. DAMMIN.*—Is it assumed that the murmur was there before the age of 8 months when the murmur was first recognized? Is this a late developmental anomaly, or is it an acquired lesion although there is no suggestion that rheumatic heart disease is present?

DR. FRIEDLICH.—It appeared so early that I assumed it was congenital in origin.

DR. DAMMIN.—Was there any suspicion that the patient might have bronchial asthma, related in some way to these recurrent infections?

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DR. PETER AULD.—This was our main concern. We wondered if this child had bronchial asthma. For this reason he was given cortisone. We thought that we could hear some changes in a few days in his auscultatory findings. This problem was not resolved.

DR. LOUIS K. DIAMOND.—The protocol mentioned a large spleen. You do not believe that this was the result of chronic decompensation in a patient with heart disease?

DR. FRIEDLICH.—I am sure that in adults you occasionally find the spleen a little enlarged, secondary to right ventricular failure. I would assume that children's spleens, like the liver, might be a little more distensible and you might see it more frequently. I think we do in acute rheumatic heart disease. It is somewhat unusual to have a spleen this large from congestion alone, and whether or not this has any added significance, I don't know.

DR. DIAMOND.—I have had the problem arise recently in several children with known congenital heart disease and periods of decompensation, who then developed low peripheral leukocyte, erythrocyte, and platelet levels, with splenomegaly. I wonder whether or not this is an independent development, or is it due to the enlargement of the spleen with resulting hypersplenism.

DR. PATRICK ONGLEY.—We do not often see hypersplenism in congestive heart failure—unless the liver itself is fairly large. We have one such case on the ward now.

Dr. Wittenborg, could the levels of the diaphragm have anything to do with the palpability of the spleen and liver?

DR. WITTENBORG.—The diaphragms are in normal position in the films. As far as the lungs are concerned, this is not the acute emphysema of a diffuse asthmatic process, but there are rather patchy areas, as we see in peripheral bronchial infection.

DR. DAMMIN.—Could we have the preoperative diagnosis and, then, the operative findings?

DR. AULD.—We believed that the child had coarctation of the aorta and bronchial asthma. We thought there was some other congenital anomaly, perhaps mitral stenosis, related to endocardial sclerosis.

DR. LESTER W. MARTIN.—I might say a word about the preoperative evaluation.

The first time we were asked to see this child, we refused to consider this baby for surgical treatment on the grounds that we did not think the child would withstand the operation. Dr. Gross thought that he did have a coarctation, but that other difficulties were more important than his coarctation. Finally, it became obvious that something had to be done, since he had been in and out of the hospital for about 9 months, with most of his time in the hospital and only a few days at home. We went ahead with the surgery, with the family realizing full well that the operative risk was at least 50 per cent. At surgery, we did the usual coarctation procedure. The coarcted segment had a pinpoint opening just distal to the attachment of the ligamentum arteriosum. The latter was completely obliterated. After the clamps were applied, we began

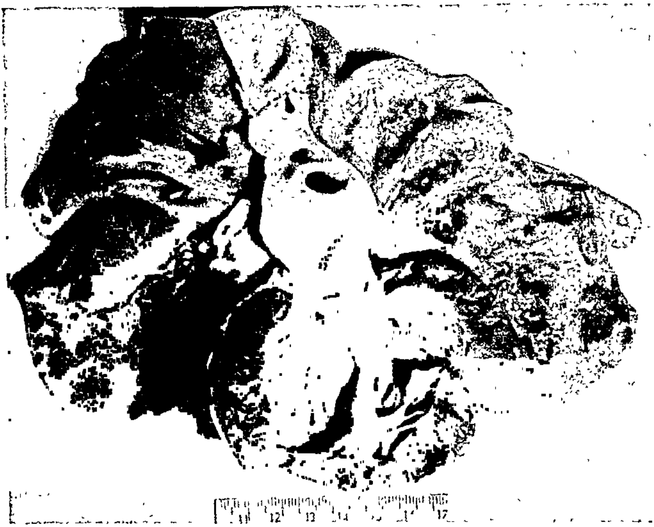

Fig. 1.—View of the left side of the heart and aorta. The anastomosis of the aorta appears intact. There is diffuse endocardial thickening and myocardial hypertrophy.

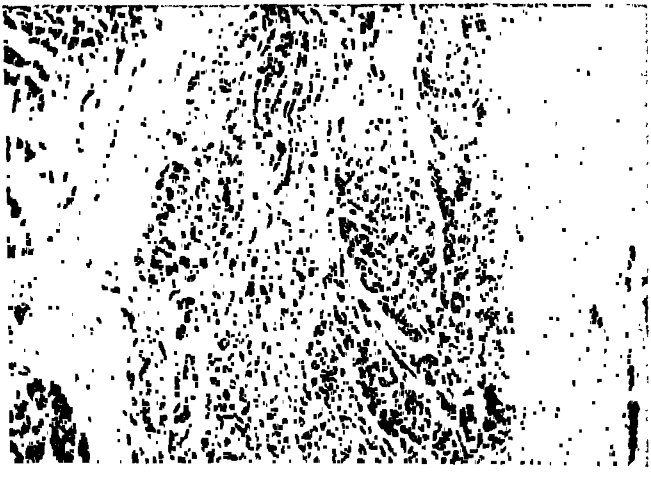

Fig. 2.—Photomicrograph of heart. The endocardium is thickened and considerable myocardial fibrosis is evident. (Hematoxylin and eosin; ×130.)

the first stitch of the anastomosis and the heart stopped beating. Cardiac massage and all resuscitative measures were of no avail.

DR. FRIEDLICH.—How much do you have to collapse the left lung in such a procedure?

DR. MARTIN.—You proceed with the operation with a fair amount of aeration of the left lung, collapsing it to 40 to 50 per cent. During the operation, if the heart begins to slow down, aeration may be increased for a period until things are in better shape. Just before we started the anastomosis, this lung had been collapsed for thirty to forty minutes.

DR. ALEXANDRE CARDOSO.—This patient had a number of congenital anomalies of the heart. The heart was markedly enlarged, bilaterally. The myocardium of the right ventricle measured 6 mm. in thickness, which is about twice normal. On the left it was 1.2 cm. in thickness. The tricuspid valve was free of any change, but there was a patchy thickening of the endocardium of the right atrium, which was markedly dilated. The pulmonary artery was 6 cm. in circumference and was dilated. The left atrium was also moderately to markedly enlarged with marked thickening of the endocardium, which was glistening white. There was a marked thickening and stenosis of the mitral valve, which measured 3.6 cm. in circumference (Fig. 1). The finger of the prosector would not pass through its orifice in the intact state. These valves were also involved by the thickening of the endocardium of the cusps with great shortening of the chordae tendineae. The endocardial surface, throughout the left ventricle, was markedly thickened, with a gray to gray-white discoloration. This appearance was borne out microscopically (Fig. 2). The aortic valve was bicuspid, with only partial formation of the septa in one of the cusps. This cusp contained two coronary ostia. The aortic arch was hypoplastic, measuring 3.6 cm. in circumference. The anastomosis was intact, and no leakage was present. There was no evidence of a patent ductus arteriosus. The lungs were markedly collapsed; the left lung occupied approximately 20 per cent of the pleural cavity and the right about 35 per cent.

The lungs were congested, with areas of bronchopneumonia. There was some thickening of the basement membranes of the bronchioles, as is seen in patients who die with asthma.

DR. DAMMIN.—In regard to the changes in the lungs, we would have to say that, if this patient did have bronchial asthma, there was no evidence that it was active at the time that he died. There were very minimal changes in the form of basal membrane thickening in the bronchi, but there was no eosinophilic infiltration and actually no microscopic or gross evidence of any prolonged evidence of obstructive episodes. We know that recurrent infection with exudation can lead to almost the same anatomic changes by the same mechanism for obstructive emphysema that bronchial asthma can, but we found no such evidence here. Therefore, we would say that this was a recurrent pulmonary infection, possibly related to a minimal degree of myocardial failure and pulmonary congestion, and that there was no other anatomic evidence here for any other lesion of the recurrent pulmonary infection.

The endocardial lesion is important. Although this can be acquired in some degree, here it is probably one of the developmental anomalies that has a great deal to do with myocardial function. Most of these patients, when they do succumb, succumb after a very short illness—usually of congestive failure, once the lesion makes itself apparent. It is interesting to note that valvular deformities are common with endocardial sclerosis, and actually most instances of congenital mitral stenosis and insufficiency are associated with endocardial sclerosis, so that in this situation one would suspect (from the clinical findings here) that endocardial sclerosis and a mitral deformity would be associated. It is interesting, also, that with this group of changes there are rarely any extracardiac congenital anomalies. There are multiple anomalies within the heart and greater vessels but, in contradistinction to the septal defects, there are very few (if any) extracardiac anomalies associated with these deformities of the type seen in this case, so that everything of importance that was observed at post-mortem examination was recognized clinically by Dr. Friedlich.

Medical Progress

RHEUMATIC PNEUMONIA

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When one considers the protean manifestations of rheumatic fever, it is not surprising that the lungs may be involved by the inflammatory process. Yet, when standard textbooks or published reports are consulted, much controversy and skepticism about this rheumatic manifestation are encountered. Even though rheumatic fever is considered a childhood disease, there is a paucity of information in the pediatric literature concerning the pulmonary manifestations of rheumatic fever. Only 5 references were found in exclusively pediatric journals.[19, 24, 56, 68, 99] The last comprehensive review on the subject[75b] was published in 1928 prior to the introduction of the sulfonamides, antibiotics, and the hormones, ACTH and cortisone.

The material presented consists of a review of the available publications about rheumatic pneumonitis. Articles are now in press, presenting (1) an analysis of the clinical and laboratory data on 23 patients with rheumatic pneumonitis, of which 21 were observed by one of the authors, and (2) a study and review of the pathologic findings in 87 fatal cases of rheumatic fever in children ranging in age between 3 and 16 years, who were patients at St. Louis Children's and Barnes Hospitals during the period 1919 through 1954.

HISTORY

In the classic review on the subject of rheumatic pneumonia, Paul[75b] stated that descriptions of polyarthritis date back to the time of Hippocrates. The valuable and most acceptable descriptions of the rheumatic syndrome date from the early seventeenth century. Paul attributed the first use of the word rheumatism to a physician in Paris, Guillaume Baillou or Ballonius, who lived from 1538 to 1616. The word rheumatism had been used previously in the sense of a weakness or indisposition, but Ballonius[3] used it to describe a condition with fever and polyarthritis which he thought could be differentiated from chronic arthritis and gout. Sydenham, in 1676, described accurately what we know as rheumatic fever and differentiated it from gout. He recognized that internal organs were affected, but said nothing specific about cardiac or lung involvement. Boerhaave[8] in 1737 referred to Sydenham's description as the best that he could find. In his description,

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Boerhaave stated that the disease invades "sometimes the brain, lungs and bowels." Störck[96] in 1762 recognized the wandering nature of the malady and also recognized that the internal organs as well as the joints were involved. He described patients with oppression of the chest, cough, and other symptoms which suggest cardiac or pulmonary disease. Störck also wrote about the earliest autopsy examinations to be found on patients with rheumatic fever. He recognized pleurisy and compression of the lungs without recognizing the cardiac lesions. Lettsom[55] in 1787 described an autopsy on a child who died of acute rheumatism with pericarditis and pleural fluid, without recognizing the associated cardiac lesions. Stoll[95] in 1788 wrote of pleural fluid in rheumatism and used the term "rheumatic peripneumonia" without giving any pathologic descriptions. Later, French writers gave little mention of his works. Chomel[15] in 1813 mentioned pulmonary involvement with rheumatism, mostly pleurisy, but was cautious not to associate them, and rather thought that the arthritis and the pleurisy were "separate afflictions." Balfour[2] in 1816 stated definitely that rheumatism was a generalized disease of fibers and membranes throughout the body, and that every blood vessel had a coat of this membrane down to the capillaries. Writing in 1840, Bouillaud[9] recognized pleurisy as a rheumatic manifestation and wrote freely about it. Grisolle[39] thought pleurisy associated with the rheumatic cardiac lesion was quite common, but pneumonia quite rare. Latham[52] in 1845 was clearly of the opinion that pneumonia occurred with rheumatism, and in a series of 136 cases of acute rheumatism, mentioned 24 with lungs "inflammed"; 18 cases were classed as pneumonia on clinical grounds. Wunderlich[107] in 1856 reported that over 6 per cent of 108 patients with rheumatism had pulmonary or pleural lesions. He discussed many clinical varieties of rheumatism. Ormerod[73] wrote in 1858 that lung involvement was a complication of rheumatism, and was usually active in causing death in such cases. Seventeen of his 61 patients had "pneumonia" and 4 of these died (no autopsy reported). He thought of the lesion as "collapse" rather than the "splenization" or "congestion" described by others. He also stated that pericarditis was a necessary accompaniment of rheumatic pneumonia. Therapy was considered useless. Vulpian[101] in 1860 described the pulmonary lesion as probably just collapse. Lebert[53], in 1860, in the German writings, recognized the pneumonia, but thought it was very rare, occurring in 1.4 per cent of 140 clinical cases. He wrote of pleurisy with accuracy and was impressed that it occurred much more frequently than pneumonia. Fuller[29] in 1864 reported 246 cases with clinical findings of pneumonia in 19, with a much larger number showing signs of pleurisy or bronchitis. He noted some pulmonary pathologic findings in almost all fatal cases of carditis. Of 16 autopsies, pneumonia was found in only 2 cases. Fuller also mentioned a case of peritonitis occurring with rheumatism. Of 41 cases, Gull[40] in 1865 found 6 with pulmonary complications, only one of which might have been pneumonia. In 1873 Pye-Smith[80] found 7 cases of pneumonia in 400 cases of rheumatic fever, 5 of which proved fatal. He regarded the pneumonia as an accidental complication of the disease, rather than an integral part of it. Sturges (quoted by Garrod[31]) in 1876 attributed the pulmonary involvement in rheumatism to two factors of that condition: (1) congestion of the lungs due to poor heart action, and (2) the fibrinous character of the blood itself which gave it a tendency to form exudates, or consolidation. Besnier[7] in 1876 credited Pitcairn (1788) as the first to associate the carditis with the rheumatism. Besnier thought the pulmonary "splenization" was an integral part of the disease and not a "complication." He thought this manifestation might be due to the cardiac lesion, however. Bernheim[6] in 1877 discussed rheumatic pneumonia, but did not distinguish between congestion secondary to cardiac failure and true pneumonitis. Peacock[76] in 1879 discussed 394 cases with 6 deaths; in one of the latter cases there were "hemorrhagic blocks" in the lungs. Pneumonia was not mentioned in any detail. Southey[93] in 1879 presented 51 patients with rheumatism, 4 of whom had clinical pneumonia. All 4 of these recovered within 6 days, none died. A bit later, in 1885, Lebreton[54] studied the pleural lesions with little attention to the pneumonia. Longstreth[57] in 1882 thought that the pulmonary affection spread from the pericardium. The pneumonia he encountered was usually mild and associated with pleurisy. He described only one autopsy with the finding of pneumonia, in which he stressed the fibrinous character of the exudate. He thought that pleurisy could occur independently of cardiac involvement. Lasegue[51] in 1884 is credited with the well-known expression that rheumatic fever "licks the joints, the pleura and meninges, but bites the heart." Mackenzie[60] in 1886 presented 133 cases and commented on the many unanswered questions about rheumatism, many of which remain currently unanswered. He commented on the cardiac and pericardial findings without associated symptoms of arthritis. Cheadle[14] in 1888 discussed an outbreak of rheumatic fever and reported 6 patients with pneumonia, and one death. The left lung was said to be "consolidated." He stressed the importance of examination of the back, even if it caused discomfort to extremely ill patients. He also distinguished between the pleurisy of long-standing heart disease (thought to be due to mechanical congestion) and that of acute rheumatic fever. Garrod[31] in 1890 reviewed several large series of rheumatic patients and found that pneumonia was encountered in 1.52 to 13.23 per cent. He thought that the pulmonary findings could be the first event in the rheumatic disease. He described the pneumonia as not substantially altering the clinical course, nor, unless severe, the prognosis. He included a discussion of acute pulmonary edema as a different entity. In 1899 Pribram[79] reported 627 cases of rheumatic fever, 4 with pneumonia, an incidence of 0.64 per cent. There was one post-mortem examination. McCrae[63] in 1903 reviewed 270 patients with acute rheumatism, among whom he found one case of clinical lobar pneumonia. Mosler[67] in 1910 stressed the generalized nature of the affection, using the term "polyserositis rheumatica." He also added the meninges and the peritoneum to the list of serous membranes affected. He did not stress the presence of pneumonia. The generalized vascular involvement in the disease was revealed by histologic studies by Klotz[49a, b] in 1912. He stressed the possibility of aneurysms on the basis of rheumatic involvement; he also found almost constant lesions in the ascending aorta. Poynton,[78] writing in 1913, thought that the etiologic agent was definitely established as the *Pneumococcus rheumaticus* and discussed it thoroughly. He spoke of bronchopneumonia surrounded by collapse; he also mentioned the presence of infarcts in the lungs. He thought that pulmonary edema was extremely rare and occurred only in children. Naish[70] in 1928 was the first to describe the histologic appearance of what we think of as rheumatic pneumonia. He considered the lesion to be specific, so specific as to suggest a specific virus. He stated he could find no earlier descriptions. Naish thought some of the changes might be early Aschoff nodules. He described many hemorrhagic alveoli, and used the term "India rubber" in describing the gross appearance of the lungs. He thought that pericarditis was not a necessary accompaniment of the pneumonia.

INCIDENCE

Accurate data concerning the incidence of pneumonia in rheumatic fever are not available. There are many reports of the clinical incidence based on the physical findings and symptoms. On the other hand, every victim of this manifestation does not die, so autopsy figures are not strictly applicable either.

A summary (Table I) of the earlier clinical reports should be adequate to point out the nature and order of magnitude of the findings.

In 1885 Howard[45] reviewed 920 published cases with the following findings: pleuritis, pneumonia, or bronchitis was recorded in 10.5 per cent of recent endocarditis cases; 58.0 per cent

TABLE I. SUMMARY OF EARLIER CLINICAL REPORTS

	CASES	PLEURISY	%	PNEUMONIA	%
1844 Taylor[97]	89	3	3.4	3	3.4
1856 Wunderlich[107]	108	5	4.6	7	6.5
1858 Ormerod[73]	61	7	11.5	17	27.8
1860 Lebert[53]	140	-	-	12	1.4
1864 Fuller[29]	246	13	5.3	28	11.4
1865 Gull[40]	41	5	12.5	1	2.5
1873 Pye-Smith[80]	400	18	4.5	7	1.8
1876 Latham[52]	136	3	2.2	18	13.2
1879 Peacock[76]	394	-	-	Not mentioned	
1879 Southey[93]	51	-	-	4	7.8
1888 Cheadle[14]	157	1	0.6	1	0.6
Three month outbreak:	26	1	3.8	6	23.2
1890 "Collective"[31]	655	13	2.0	11	1.5
1903 McCrae[63]	270	6	2.2	1	0.4
1920 Rolly[87]	3620	88	2.5	51	1.4
1927 Schwartz[88]	53	-	-	5	9.5
1928 Howard[44]					
Arthritis	96	7	7.3	0	0.0
Rheumatic cycle	130	20	15.3	6	2.7
1931 Coburn[17a]	162	8	4.9	11	6.8
1933 Howard[43]	489	-	-	9	1.8
1945 Plummer[77]	54	(Streptococcal sore throat)		1	1.9
1947 Rantz[82]	69	(Poststreptococcal state)		3	4.3
1947 Sokolow[92]	-	-	-	-	2.0
1954 Reimann[84]	"Severe rheumatic fever"		-	-	1.0

of pericarditis cases; 71.0 per cent of endopericarditis cases; and 7.0 per cent of cases without heart disease.

The incidence in pathologic material varies considerably depending on the rigidity of the criteria used in making the diagnosis. Many series were reported in which only the gross specimens were evaluated (Table II).

In spite of the inadequacy of available figures it has been frequently mentioned that pneumonia is an important manifestation of rheumatic fever, and an important contributor to the death of these patients. Gouley[33] stressed that the pulmonary involvement was as frequent as the cardiac involvement. Griffith[37] said that pulmonary disease is second only to carditis in importance. It might be stressed that pneumonia is not frequently seen in a series of patients with moderately severe clinical rheumatism, but that it is very likely to be

TABLE II. INCIDENCE OF PNEUMONIA IN REPORTED SERIES

<table>
<tr><th></th><th>CASES</th><th>FINDINGS</th></tr>
<tr><td>1925 Thayer[98]</td><td>25 fatal cases of rheumatic fever
10 with "terminal pneumonia"</td><td>Incidence 40%
Lungs were poorly studied histologically</td></tr>
<tr><td>1928 Paul[75b]</td><td>30 deaths</td><td>10-50% with pneumonia</td></tr>
<tr><td>1929 McClenahan[62]</td><td>28 fatal cases of rheumatic fever</td><td>Pleurisy 64%
Pericarditis 75%
Hemorrhagic pneumonia common
Bronchopneumonia "uncommon"
Infarction in lungs 21.4%</td></tr>
<tr><td>1933 Coburn[17b]</td><td>320 deaths</td><td>45 (14.1%) had "hemorrhagic pulmonary solidification"</td></tr>
<tr><td>1941 Epstein[23]</td><td>14 deaths during first attack</td><td>7 had "hyaline membranes" 50%</td></tr>
<tr><td></td><td>10 deaths in cases with previous attacks; died in less than 3 weeks</td><td>5 (50%) had pneumonia</td></tr>
<tr><td></td><td>11 deaths in cases with previous attacks; died in 3 to 6 weeks</td><td>4 (36.3%) had rheumatic pneumonia
5 (45.5%) had bacterial bronchopneumonia</td></tr>
<tr><td></td><td>10 deaths in cases with previous attacks; present attack over 6 weeks</td><td>2 (20%) had "hyaline membrane"
5 (50%) had bacterial bronchopneumonia</td></tr>
<tr><td>1946 Griffith[38]</td><td>Reported the following percentages without giving his criteria for diagnosis of pneumonia:</td><td><table>
<tr><th></th><th>RHEUMATISM</th><th>PNEUMONIA</th><th></th></tr>
<tr><td>Acute fulminating</td><td>52</td><td>28</td><td>53.1%</td></tr>
<tr><td>Polycyclic</td><td>281</td><td>77</td><td>27.4%</td></tr>
<tr><td>Monocyclic, subacute</td><td>667</td><td>14</td><td>2.0%</td></tr>
<tr><td></td><td></td><td></td><td>11.3% of total</td></tr>
</table></td></tr>
<tr><td>1944 Neuburger[71]</td><td>63 post-mortem examinations</td><td>8 (12.7%) had distinctive microscopic changes of rheumatic pneumonia</td></tr>
</table>

found in patients who die of acute rheumatic fever.

ETIOLOGY

As early as the eighteenth century it was implied that the whole body was involved in the rheumatic disease,[3] but this probably merely represented a statement of opinion in terms of the humoral theory of disease and did not indicate insight into what we now think of as a generalized vascular disease.

In the evolution of the more recent concepts of the etiology of rheumatic fever it is to be expected that a microbic or viral etiology would be suspected. Without implying that any specific organism or process was involved, Longstreth[57] in 1882 was the earliest to speak in terms of "spread" of the disease. He thought that the lung involvement was an "extension of inflammation from pericardium to lung." Burnet[10] in 1947 called attention to the fact that he had stated in 1905 that "pneumonia may be caused by the specific organism of rheumatism." Coombs[20a] stated definitely in 1909 that rheumatic fever must be a "microbic" disease. Just a few years later, in 1913, Poynton and Paine[78] produced a large monograph in which they described the discovery and bacterial characteristics of an organism, *Diplococcus rheumaticus,* which they were confident was the specific etiologic agent of rheumatism. Hutchison[46] in 1922 also wrote that the pneumonia was an extension to the lungs, and was always associated with pericarditis, the implication being that an organism of some sort performed the extension.

Schwartz[88] wrote of rheumatic fever producing a vulnerability to infection or reactivation of a latent infection, without specifying what sort of organism might be involved. Naish[70] in 1928 disagreed with the belief in the necessity for extension of the disease from the pericardium, or even for the necessity of concomitant pericarditis to occur. He thought that the disease was caused by a virus. Rabinowitz[81] spoke just of the rheumatic virus in 1926, two years earlier than Naish. More recently, Geever[32] in 1951 and Shopfner[91] in 1952 have mentioned the possibility of rheumatic pneumonia being the result of a virus infection. Neither bacterial nor viral studies, however, have ever been fruitful in establishing a microbic, infective agent as having a significant role in rheumatic fever or the characteristic pneumonia sometimes accompanying rheumatism.

Melnick[65] wrote that the pathologic findings had some resemblance to allergic granulomas. Rich[83] also thought that the pathologic findings were quite similar to those of sulfonamide anaphylactic pneumonia. Cook[19] thought that perhaps some nervous control of the lungs was altered by the frequently associated pericarditis.

Currently there are diverse opinions concerning the etiology of rheumatic pneumonia. The most likely were mentioned by Seldin[90]:

1. The pneumonia is a part of the rheumatic process.
2. The pneumonia is secondary to the cardiac lesion or cardiac failure.
3. Intercurrent infection is the basis for the pneumonia.
4. The syndrome is a combination of No. 1 and No. 2.

As early as 1816 Balfour[2] wrote that rheumatic fever was an affection of the muscular fiber or of "cellular membrane" which coats all the blood vessels of the body, even the "minutest capillary." Rolly[87] in 1920 wrote of the disease as a disease of the serous membranes. He thought it could not be considered as a "complication" but was an integral part of the rheumatic disease. Pappenheimer[74] in 1927 emphasized the presence of specific rheumatic lesions in peripheral blood vessels which he thought were as characteristic as the Aschoff nodule in the heart muscle. Gouley[33a] in 1937 wrote that the lungs were probably as commonly involved in the rheumatic process as the heart. He mentioned several reasons, however, why the cardiac lesion might be deleterious to lung function on a mechanical basis. Epstein[23] in 1941 thought that many of the pathologic findings in rheumatic lungs were attributable to capillary vascular damage.

Because of the usual intimate concurrence of pneumonitis with carditis, many writers have stressed that the pulmonary findings, mostly clinical, are secondary to cardiac functional impairment. Besnier[7] reported in 1876 that the pneumonia probably was not a true pneumonia, but pulmonary engorgement or "splenization," secondary to the heart lesion. Garrod[31] in 1890 studied 1,066 cases of "acute pneumonia" and found cardiac valvar lesions in only 10. He thought this was evidence that the pneumonia of rheumatism had little connection with the cardiac involvement of that disease. Although Coombs[20b] in 1924 listed collapse as a separate phenomenon from pneumonia, he pointed out that many cardiac disturbances could produce the physical signs of pulmonary disease. The frequent finding of left lower lobe collapse he attributed to either: (1) pressure from the enlarged heart on the lung, (2) immobility of the diaphragm produced by a reflex from the inflamed pericardium, or (3) atelectasis due to pressure on bronchial structures. He was careful to warn about the danger of confusing atelectasis with true pneumonic consolidation. Findlay[24] in 1930 presented 25 clinical cases of rheumatic fever with pulmonary complications. He was convinced that all cases had associated carditis, and that the pneumonia which he occasionally encountered was a "complication," either bacterial lobar pneumonia or terminal hypostatic bronchopneumonia. Interestingly enough he characterized the pleural fluid as a "transudate," in disagreement with most descriptions of this fluid. Gouley[33a] in 1937 attributed the basal pulmonary collapse to several associated difficulties seen in the patient with acute rheumatism, i.e., pleural effusion, pericardial fluid, diaphragmatic paralysis, supine position in bed, and/or cardiomegaly.

As far as the concept of the pneumonia as a bacterial infection is concerned, there is no clinical, cultural, or pathologic evidence to support such an etiology if one confines himself to the characteristic picture of rheumatic pneumonia. Surely some patients with terminal rheumatic fever *must* have bacterial pneumonia; patients with pulmonary edema are prone to have secondary bacterial infections. Paul[75b] and Gouley,[33a] however, both stress the fact that a bacterial pneumonia is distinctly uncommon in autopsy examination of patients who die of acute rheumatic fever, even before the use of antibiotics.

Most pathologists who have written on rheumatic fever or rheumatic pneumonia seem to lean to the theory that all the manifestations of rheumatic fever are a reflection of a vascular reaction of some unknown type, probably hypersensitivity, and probably related in some way to hemolytic streptococcus infection. Keefer[48] and more recently Rantz[82] in 1947 have written of the protean clinical findings which they term the "poststreptococcal state." Currently we must await more specific information about the complicated serologic and cellular mechanisms which produce the full-blown, catastrophic, explosive rheumatic syndrome at times, and the limited, migratory, protean "poststreptococcal" syndrome at other times.

CLINICAL FEATURES

It is impossible to define a clinical syndrome which would be specific for rheumatic pneumonia. The circumstances which would call the clinician's attention to such a possibility would be pulmonary complications in a child with known rheumatic fever presenting with carditis, arthritis, chorea, or some other definite rheumatic manifestation. Seldin[90] stated that carditis must always accompany rheumatic pneumonia. Some observers, however, have found pneumonic involvement characteristic of rheumatic fever, but without evidence of other elements of the rheumatic syndrome.

Descriptions of the disease often stress the paucity of signs and symptoms compared with the pathologic or roentgen-ray changes found. Writing in 1888, Cheadle[14] discussed 6 cases of pneumonia associated with rheumatic fever. In 5 of the 6 there was "no cough, no rusty sputum, nothing but the rise of temperature and quickened respiration." He warned the clinician, "whenever pericarditis arises in the course of rheumatic fever, or whenever an unexplained rise of temperature, or persistence of high temperature occurs, make a careful examination of the physical condition of the chest, behind as well an in front." Garrod[31] also warned that the back should be examined in the patient with rapid rise in temperature, often transitory, without cough or sputum. Rabinowitz[81] counseled that examination of the back should not be neglected in acute rheumatic fever.

The majority opinion is that it is necessary to have diagnosed rheumatic fever in the acute stage before one can safely diagnose rheumatic pneumonia. Several authors have stated, however, that pulmonary alterations by the rheumatic process can occur as isolated manifestations in rheumatism. Gouley[33a] stated that the "involvement of the lung to some degree in rheumatic fever is as common as that of the heart." He thought that the pulmonary changes were not a complication, but rather an integral part of the rheumatic process, which might precede or occur without arthritis. Goyena[35] reported his experience of finding lung manifestations preceding rheumatic arthritis and endocarditis. Lees[59] reported 2 cases of pulmonary consolidation occurring with acute polyarthritis, but without cardiac involvement by clinical and electrocardiographic evaluation. One of the 2 patients later appeared with mitral valvar disease, however. Rabinowitz[81] thought of rheumatic pneumonia as a special pneumonopathy usually occurring with pancarditis, but occasionally occurring in the absence of arthritis or carditis. Rantz[82] reported 3 cases of pneumonia occurring in the "poststreptococcal state." One patient was without arthritis, one had only pain in the chest, and the third had no physical signs at all, but was found to have patches of infiltration in the roentgenogram of the chest. Van Wijk[99] reported 3 cases; in the only survivor the onset of the illness was with pulmonary symptoms. Thus it appears that it is not always necessary to have a classic rheumatic syndrome with carditis before involvement of the lungs with pneumonia.

Once the lungs have been involved by the pneumonic process the clinical features are so variable and descriptions so at odds that one can only mention some of the features which previous writers have stressed. It would be useful to the clinician to know in which type of case pneumonia would be most likely to occur.

Griffith and associates[38] are the only writers who made a systematic attempt to analyze the type of rheumatic fever which is likely to be associated with pulmonary involvement. They found that pneumonia was encountered (their criteria for diagnosis were not given) in 53.1 per cent of cases of "acute fulminating rheumatic fever," in 27.4 per cent of "polycyclic" rheumatic cases and in only 2.0 per cent of "monocylic, subacute" cases. Their over-all incidence was 11.3 per cent, a widely quoted figure. Elsewhere in the literature there is little or no mention of the type of case where the suspicion of rheumatic pneumonia must be increased. Reimann[81] stated that it occurred in a small proportion (1 per cent) of "severe rheumatic fever" patients.

There is mentioned a peculiar disproportion between the change in the clinical condition of the rheumatic patient who has developed pneumonia and the physical findings which might be encountered. Often a thorough examination of the chest by routine physical diagnostic techniques reveals nothing to explain the sudden change in the temperature, respiratory rate, and cough.

Cough is a frequently mentioned symptom. Usually it is hacking in nature and without production of sputum.[90] A small number of writers have minimized the cough. Reich[83] stated that cough and sputum were not prominent. Coburn[17a] thought of the pneumonia as a solidification "without cough or sputum." In fact, he minimized the clinical changes with the description that the pneumonia was a "migratory, pulmonary solidification which appeared during severe acute carditis, not resembling pneumonia of known bacterial origin, not accompanied by cough or sputum in most instances, not associated with heart failure or atelectasis due to compression."

The absence of sputum, even where cough is present, is universally agreed upon. If a small amount of sputum is produced, it may be blood streaked or rusty.[90]

Tachypnea is probably the most common and most characteristic indication that a pneumonic process is occurring in a patient with rheumatic fever. The tachypnea may be accompanied by profound distress (dyspnea) if the process is fulminating and overwhelming,[90] or it may be present without disturbing the patient's comfort at all.

So filled with inconsistency are the descriptions that Coburn[17a] thought there was no effect on the respiratory rate; Howard[43] thought there was a "slight elevation in respiratory rate." Conversely, Wilson[105] classed the increased respiratory rate with the fever and cough as important clinical changes when pneumonia occurred. Cheadle[14] said there may be "no cough, no rusty sputum, nothing but the rise in temperature and quickened respirations" to signal the pneumonia.

Other observers were impressed with the dyspneic respirations. Fuller,[29] writing in 1864, characterized the disease as "attacking sometimes one, sometimes another part of the pulmonary structure, sometimes invading all parts simultaneously, producing dyspnea, suffocation and death." On the other hand, Hadfield[41] stated that usually dyspnea was absent, or was seen only in the presence of congestive heart failure. In 1950 Lustock[58] wrote of the septic fever, hemoptysis, dyspnea, and orthopnea which were out of proportion to the physical findings and which did not occur with congestive failure, did not respond to digitalis or mercurial diuretics, and were not the result of overdosage of salicylates.

The occurrence of pleuritic pain as a symptom is in some question also. Garrod[31] stated that pleurisy is the "earliest even in the rheumatic series." One must be careful in evaluating pleuritic pain because many rheumatic manifestations could produce such pain without the presence of pneumonia, i.e., pericarditis, pleuritis, or pulmonary infarction. Gouley[33a] thought that pleural pain was rare. Longstreth[57] thought pleurisy was more common than pneumonia. In 1882 he said, "the gravity of the condition [pneumonia] was of slight character and usually associated with pleurisy." Myers[69] found pulmonary involvement in addition to the pleurisy in 5 of 13 cases of rheumatic pleurisy. He stated that the dyspnea and orthopnea were out of proportion to the physical findings. Seldin[90] stressed pleuritic pain as a differential point favoring rheumatic or bacterial pneumonia as opposed to pulmonary edema.

Although a classic symptom of bacterial pneumonia, chill is rarely or never found in rheumatic pneumonia.[33a]

In cases of acute rheumatic fever with generalized involvement one must be aware of the unusual complications of peritonitis[29, 83] on a rheumatic basis, or even cerebral involvement.[102]

The physical examination is often of little more aid than the enumeration of the symptoms of the patient. Descriptions are filled with such terms as shifting, evanescent, migratory, transient, insidious, fleeting. Neubuerger[71] in a review in 1944 wrote of the disease as a suddenly occurring one with fever, cough, bloody sputum, and elevation of white cell count, and severe dyspnea. Ormerod[73] in 1858 wrote that the general condition of the patient grew worse, and he thought that signs of pericarditis accompanied the pulmonary signs. Fever of greater severity than is usually seen in the patient with acute rheumatism is widely described.[90] Gouley[33a] and others stressed the suddenness of the increase in temperature. Naish,[70] however, minimized the prevalence of change in temperature.

The pulse rate probably depends more on the underlying cardiac disease than on the pneumonic process. Coburn[17a] stated that the pulse is little altered by the rheumatic pneumonia.

The majority of descriptions of the clinical findings mentioned the fleeting nature of the pneumonic involvement. Caffey[11] said the roentgen-ray shadows are "fleeting and migratory." Coburn[17a] termed the pneumonia "flighty" and thought that it usually "disappears completely before death." Epstein[23] stated there is "rapid disappearance of symptoms within a few days" with a migratory and fleeting character to the consolidation. In 1890 Garrod[31] stated the pneumonia was "transient." Others[33a, 34, 37, 43, 58, 59, 81, 83, 84, 105, 131] specifically commented on the transient, migratory nature of the pulmonary involvement. Lees[59] did differentiate a more severe, more extensive consolidation of the lower lobes which may last for weeks or months. Melnick[65] concisely summarized the usual description as "migratory, areas of consolidation in the lung fields which appear suddenly, last a variable length of time, disappear as quickly and unexpectedly as they appear, and produce no change in the clinical picture and no variation in the pulse or respiratory rate."

Whether the physical findings in the chest indicate congestion or solidification or other pathologic conditions is open to variable opinions. Coburn[17a] characterized the pulmonary features of rheumatic fever as solidification. Gouley[33a, 34] indicated that the physical findings were those of consolidation, but that the roentgenogram interpretation was frequently that of "pulmonary congestion." Lustock,[58] in a discussion of clinical and pathologic correlation, stressed the difficulty of clinical diagnosis, but referred to pulmonary consolidation.

The distribution of the lesions as determined clincally is commented on by a number of writers. Bamberger[4] in 1857 described a patch of dullness on the left posterior chest at the angle of the scapula which spread over the left base in cases of pericarditis, pleuritis, and collapse. No mention of pneumonia was made, but later writers mentioned Bamberger's sign in connection with pneumonitis of the left lower lobe. Longstreth[57] in 1882 said that the left side was more frequently involved than the right, but offered no explanation for this. Naish[70] mentioned Bamberger's sign only to contradict the impression that the left was more vulnerable. He warned against stressing one-sideness. His conclusions were supported by autopsy findings. Griffith[37] described small areas of dullness with decreased breath sounds which might occur anywhere in the lungs. Lees[59] in 1952 discussed the rheumatic lung as following two courses. One was an extensive consolidation usually in the lower lobes and lasting weeks to months; the other was focal, multilobular, evanescent, migratory in nature; and either might produce death. Gouley[33a] stressed basilar collapse, probably more frequently seen on the left. This collapse was attributed to inflammation with loss of elasticity, air absorption, and contracture, caused by interstitial pneumonitis. Other manifestations of the diffuse rheumatic condition which could lead to basilar collapse are effusion, pericardial fluid, cardiomegaly, collapse secondary to bed rest, and/or poor diaphragmatic movement on the pleuritic side. All such factors must be considered in the rheumatic patient with abnormal pulmonary findings. Earlier Gouley[34] had described 9 fatal cases with consolidation in 8, without the demonstration of preference for any particular lobe.

The signs and symptoms of cardiac decompensation are similar to those generally ascribed to pneumonia in rheumatic fever. Coburn[17a] stated that the pneumonia was found in the absence of heart failure or atelectasis. Garrod[31] in 1890 mentioned the left-sided occurrence of pneumonia or "compression," but discussed acute pulmonary edema as found in heart failure as a separate entity. Gouley[33a] thought that usually heart failure was absent. Fraser[27] stated that the signs and symptoms are usually attributed to other diseases than rheumatic pneumonia, such as cardiac failure, pleural effusion, paralysis of the diaphragm, or pressure on the lung by heart or fluid. On the other hand, Seldin[90] thought that cardiac failure was present to some degree in all patients with rheumatic pneumonia.

As in all cases of rheumatic fever, the involvement of the heart is to be feared. Pneumonic involvement may occur with or without cardiac involvement, but, without the heart changes, a clinical diagnosis is very weak. Rabinowitz[81] stated that the pneumonitis usually occurs with pancarditis, but could be independent of arthritis or carditis. Howard[45] stated in 1885 that about 7 per cent of patients had pulmonary affections without cardiac disease. He described the evanescent and obscure findings in rheumatic pneumonia, but he pointed out that in rare instances the pneumonia definitely alternated with arthritis in the rheumatic patient. Jensen[47] reported a case of rheumatic pneumonia without carditis.

Cyanosis is rarely mentioned as a dependable indication of the pneumonic process. Seldin[90] is alone in stating that cyanosis is constantly present, along with dyspnea and orthopnea.

Pulmonary complications of rheumatic fever which might be confused with pneumonia and which should be searched for in the patient with acute rheumatism are numerous. Coombs[20b] discussed pleurisy, basal collapse, acute pulmonary edema, as well as pneumonia. Findlay[24] studied the conditions which occur with rheumatic pericarditis and listed several cases of pleural effusion, lobar pneumonia, and passive congestion, but did not believe in the entity of a true rheumatic pneumonia. He stated that pulmonary complications do not occur without carditis, but it must be noted that his approach was to study carditis rather than other conditions of the thoracic viscera. Rabinowitz[81] thought of pneumonia as a separate entity but listed many possible manifestations of pulmonary disease to be aware of in severe rheumatism: fibrinous pleurisy, pleurisy with effusion, atelectasis with or without effusion, hydrothorax secondary to cardiac failure, acute pulmonary edema, chronic passive congestion, hemorrhagic static infarction of the lung, or embolic infarction of the lung.

Widal[104] made a unique suggestion that it was possible for the rheumatic process to involve the veins of the lower extremities and lead to embolization to the lungs.

Gouley[33a, b] was of the belief that the long-term result of pulmonary involvement with pneumonia was the etiologic factor in pulmonary fibrosis and right heart strain seen in the older rheumatic patient. Moschcowitz,[66] however, did not mention rheumatic pneumonia or fibrosis secondary to rheumatic involvement of the lung as a cause of pulmonary hypertension, but he wrote this several years before Gouley advanced his concept.

DIFFERENTIAL DIAGNOSIS

In the foregoing section, several complications of the rheumatic state which might lead to pulmonary manifestations are mentioned. These conditions must be considered in acute rheumatism with abnormal findings in the pulmonary structures. There are several diseases, however, which are quite distinct from rheumatic fever, but which could be confused with rheumatic pneumonia, or, conversely, may be rheumatic pneumonia but are diagnosed as another disease.

Caffey[11] wrote that rheumatic pneumonia should be chiefly distinguished from cardiac failure and bacterial pneumonia. Griffith[38] stressed the confusion possible with other pneu[illegible]ias, ei[illegible]ial or viral. Lees[59] probably had the most complete list of conditions which must be considered when one is confronted with a patient with acute polyarthritis and pulmonary manifestations. His list included: (1) bronchial carcinoma, (2) pulmonary tuberculosis, (3) bacterial pneumonia, (4) bronchiectasis, (5) viral and rickettsial diseases, (6) coccidioidomycosis, (7) subphrenic abscess, (8) asthma, (9) angioneurotic edema, (10) periarteritis (polyarteritis) nodosa, (11) Löffler's pneumonia.

Seldin[90] presented a chart to show the differential between the two most frequent diseases resembling rheumatic pneumonia.

Kneeland and Smetana[50] in 1940 reported 52 cases of bronchopneumonia of unusual character and unknown etiology. There were cases with other manifestations such as migratory polyarthritis, skin rashes, hematuria, fibrinous pericarditis, and encephalitis, any of which might have been cases of rheumatic fever of a bizarre character. Only one such patient died and the descriptions of the organs were entirely commensurate with a diagnosis of rheumatic pneumonia.

DIFFERENTIAL DIAGNOSIS BETWEEN ACUTE PULMONARY EDEMA, RHEUMATIC PNEUMONIA, AND BACTERIAL PNEUMONIA*

SYMPTOMS	ACUTE PULMONARY EDEMA	RHEUMATIC PNEUMONIA	BACTERIAL PNEUMONIA
Active carditis	Not necessary	Always	Rare
Fever	Plus or minus	High	High
Pleurisy	Absent	Frequent	Frequent
Dyspnea	Profound	Profound	Depends on pulmonary signs
Sputum	Pink, frothy	Mucoid, blood streaked	Purulent
Physical signs	Marked	Few	Moderate to marked
X-ray			
Distribution	Nonsegmental	Nonsegmental	Segmental, lobar
Lobes	Multiple, bilateral	Multiple, bilateral	Rarely more than 2 to 3
Type	Soft, hazy, patchy	Soft, hazy, patchy, linear, reticular	Dense, homogeneous
Pathogens in sputum	None	Usually none	Present

*From Seldin, Kaplan, and Bunting.[90]

Atypical virus pneumonia is another disease which might be confused with, or diagnosed instead of, rheumatic pneumonia. Anderson[1] stated that the microscopic picture of rheumatic pneumonia resembles virus pneumonia. Finkelstein and Klainer[25] reported 3 cases of virus pneumonia with pericarditis and all patients recovered. They attributed the pericarditis to the virus of pneumonia. They mentioned the possibility of rheumatic pneumonia but hesitated to diagnose that disease because their cases were mild, the pneumonia persisted (they thought of rheumatic pneumonia as transient), no murmurs were heard, and the electrocardiograms were not typical of rheumatic fever. None of these reasons is valid for excluding rheumatic pneumonia. Jensen[47] believed that many cases of atypical virus pneumonia were really cases of missed rheumatic pneumonia. He reported a case with hemorrhagic nephritis, arthritis, pneumonitis, without cardiac involvement. He stressed the accompanying rheumatic manifestations in rheumatic pneumonia and the value of the antistreptolysin titer in that disease, and that the cold agglutinins should be elevated in virus pneumonia. McKinlay[64] reported 2 cases (with one death) of atypical pneumonia with rheumatic endocarditis. He discussed the possibility that this might have been rheumatic pneumonia, but did not believe the process was a specific one.

Pulmonary congestion from chronic valvular disease is easily confused with other pulmonary manifestations, and must be considered seriously in the older rheumatic patient. Anderson[1] mentioned the possibility of confusion between rheumatic pneumonia and the congestion secondary to mitral disease.

Clark and Kaplan[16] described the changes in tissues associated with serum disease in man. The diffuse arteritis of that condition leads to many manifestations which might cause confusion with rheumatic pneumonia, e.g., arthritis, fever, pneumonitis, skin rashes.

Vascular allergy in the pathogenesis of asthma was discussed by Harkavy,[42] who reported 8 cases of asthma with migratory inflammatory, interstitial lesions of the lungs. In 6 there were pleural effusions; in 3, pericardial involvement also. The electrocardiogram was abnormal in 6 of the 8. Such cases could easily be confused with cases of rheumatic pneumonia. Cole and Korns[18] reported a case which presented many manifestations of angioneurotic edema. There was no autopsy, but rheumatic fever, Löffler's pneumonia, and polyarteritis nodosa were not ruled out in this bizarre case. At various times the patient had edema of the hands, forearms, feet, and face; dyspnea; tachypnea; pulmonary edema; pulmonary infiltration; fever; headache; lymphadenopathy; and vague skin rashes but no joint symptoms. There was an eosinophilia of 50 to 80 per cent. Vaughan and Hawke[100] reported upon a man with angioneurotic edema who suffered from repeated and extremely varied symptoms attributed to allergy. Among these symptoms were meningismus, headache, hydrarthrosis, symptoms of appendicitis, sinusitis, pulmonary edema, and pulmonary infiltration resembling miliary tuberculosis which cleared after an Adrenalin injection.

Elkeles[22] reported a case with changing roentgen-ray manifestations in the lungs, fever, arthritis, eosinophilia, and neurologic changes. Clinically the author did not rule out rheumatic fever, Löffler's pneumonia, or angioneurotic edema. At autopsy, however, the patient was found to have polyarteritis nodosa. Friedberg and Gross[28] reported 8 cases of polyarteritis nodosa in 4 of which there was evidence of rheumatic heart disease by the presence of Aschoff nodules in the myocardium. They suggested that rheumatic fever might be a cause of polyarteritis nodosa. Pneumonia was not discussed. It might be more reasonable to say that rheumatic fever probably resembles polyarteritis clinically and pathologically. Weir[103] reported a case with asthma, skin rash, cardiac disease, renal disease and eosinophilia as a case of polyarteritis nodosa. The descriptions of the roentgen-ray findings resembled those reported in rheumatic pneumonia: "The hilar shadows are increased in width with marked increase in the lung markings, particularly in the hilar regions and lower lung fields."

Woodland[106] reported a case of a 16-year-old boy with rheumatism, pulmonary opacity, increased sedimentation rate, pericardial friction rub, tic-tac cardiac action, pleural rub and effusion, which, after six negative examinations for acid-fast organisms, was finally diagnosed as tuberculous rheumatism. In general tuberculosis should not be confused with rheumatic pneumonia. Neubuerger and associates[71] cited one proved case of rheumatic pneumonia which had the distinctive roentgen picture of miliary tuberculosis.

LABORATORY AND ROENTGENOGRAM

Other than the laboratory findings of acute rheumatic fever, rheumatic pneumonia presents no special laboratory features. As in acute rheumatic arthritis, carditis, etc., one might expect to find an elevation in the total white-cell count, with a preponderance of polymorphonuclear cells. There is often an anemia of mild degree, the cause of which is not understood. Platelets and other cellular elements are normal. The erythrocyte sedimentation rate is almost always elevated. If more complicated procedures are available, it may be found that the antistreptolysin, and the antihyaluronidase titers are elevated, just as in the simpler cases of acute rheumatic fever.

Changes in the cellular elements of the urine may be encountered, red blood cells being present in the sediment, and there may be proteinuria. These urinary changes probably reflect the generalized vascular involvement in severe rheumatism. The urinary changes are found more frequently in severe cases with pericarditis, pneumonia, myocarditis, than in the less severe cases of acute rheumatism.

The electrocardiogram may be abnormal, just as in other rheumatic patients. Lustock,[58] in reporting 12 necropsy-proved cases of rheumatic pneumonia, stated that the ECG evidence of progression was invariably present.

In recent decades, since the virus or bacterial etiology of rheumatic fever is no longer widely held, all authors agree that there are no consistent bacteriologic findings in rheumatic pneumonia. Neubuerger[71] studied 8 distinctive cases at autopsy with negative bacteriologic studies of the lungs. Bacteriologic studies have been attempted and reported repeatedly by many authors,[62, 72, 75b, 90, 109] all with negative results. Studies of the pleural fluid for organisms directly or on culture have been negative.[79, 87]

Sabrazes (according to Paul[75b]) did cell counts of the pleural fluid of patients with acute rheumatism without arriving at any definite conclusions. He reported finding endothelial cells with polymorphonuclear cells during the acute disease.

Perhaps the most helpful clinical examination is the roentgenogram of the chest. Caffey[11] characterized the chest roentgenogram as "fleeting and migratory" and said that many lobes may be simultaneously involved. Gouley[33a] warned that often the roentgenograms were interpreted as "passive congestion." Griffith[38] pointed out the patchy, shifting nature and mentioned the resemblance to pulmonary infarction. Pleurisy may also be seen. Levy[56] stressed the fleeting character. Lustock[58] described many roentgenographic findings in cases coming to autopsy: consolidation, hilar engorgement, edema, peribronchial nodules. He pointed out, as have others, that the roentgen-ray findings did not parallel the clinical course or findings. Neubuerger,[71] on the other hand, minimized the value of the roentgen ray. He found only one case in 8 that had roentgenograms of diagnostic value. One of his patients had chest films which resembled those in miliary tuberculosis. Rantz[82] described 3 cases of "poststreptococcal" pneumonia diagnosed by roentgen ray. In one of these cases the roentgenogram was normal on the day that chest symptoms were prominent; the roentgen-ray changes in the lungs appeared later. Reimann[84] mentioned the patchy, transient, shifting nature of the roentgen-ray findings, as well as the possibility of lobar consolidation, atelectasis, and pleural fluid.

Schwedel[89] gave a complete discussion of the roentgen-ray findings in rheumatic fever. These include: pulmonary congestion, either vascular or interstitial; pleural effusion; infarction; acute pulmonary edema; chronic pulmonary edema; pneumonia; fibrosis; and pleural thickening. Seldin[90] and Schwedel[89] both stressed the "butterfly" distribution of the infiltration about the hilar regions with a peripheral clear zone. Weir[103] described similar findings in polyarteritis nodosa. Woodland[106] described roentgen-ray findings in the lungs resembling infarction, later going on to pleural effusion and lobar consolidation in a case of tuberculous rheumatism.

PROGNOSIS

The prognosis of the patient who develops rheumatic pneumonia is difficult to determine. As in other diseases, one may predict on the basis of the findings in the individual case, complemented by what is known of the over-all experience in a large number of clinical cases. It is interesting to note the statements of various authors as to their experience regarding prognosis.

Rabinowitz[81] stated that rheumatic pneumonia was a "pneumopathy of fleeting character which did not influence prognosis," and which "rarely causes death." One of the earliest writers to describe pneumonitis was Naish[79] who stated in 1928 that the pulmonary features "do not usually appear to add much to the gravity of the prognosis, and the great majority live for the dullness to clear up." In 1950 Lustock[58] stated that the manifestations of pneumonitis did not produce a syndrome which was uniformly fatal and that frequently the "complication" was not recognized until autopsy.

The authors who had little fear of pneumonia in rheumatic fever are in the minority, and most writers dreaded this manifestation. Latham[52] in 1845 said that "such forms of pulmonary inflammation are portentous ingredients in the clinical history of acute rheumatism, and give a fearful interest to it." Ormerod[73] in 1858 wrote that the pneumonia usually was a prominent feature in the cause of death in acute rheumatism. He thought therapy was useless. Fuller[29] in 1864 wrote that "its appearance is fraught with unusual danger." He stressed that in almost all fatal cases of carditis one would also find pleurisy or pneumonia or both present. Pye-Smith[80] in 1873 thought of the pneumonia as an accidental complication rather than a fundamental part of the rheumatic state, but he thought it was one of the "most frequent causes of death." Garrod[31] in 1890 thought that in milder cases the prognosis was no worse than that usual in rheumatism, but stressed the hazard of extensive, "especially double pneumonia." Griffith[37] in 1947 wrote that pneumonia was second to carditis in importance because of its frequency, its relationship to right-sided heart failure, and because it was an important cause of death. Seldin[90] thought the prognosis very grave because all 6 of his reported cases were fatal.

Gouley[33a] formulated the concept that the prognosis might be unfavorable in other ways than by increasing the death rate in acute rheumatism; that is, he wrote, that rheumatic pneumonia might be the cause of chronic, fibrotic changes in the lung which eventually would lead to right-heart strain and thus to a chronic complication of the rheumatic syndrome. Reimann[84] in 1954 wrote that the pneumonia might lead to chronic fibrotic changes in the lungs, resulting in protracted cardiac difficulties.

It may be said that the prognosis of rheumatic pneumonia is not clearly known, but that probably it is not always fatal. With more thorough search for rheumatic pneumonia and with improved therapy, many more cases of this disease may be seen which do not terminate in death.

TREATMENT

Antibiotic and chemotherapeutic *agents have not proved to have any* specific effect on the pulmonary manifestations of the rheumatic syndrome. This is not to say that these agents may be omitted, primarily because of the difficulty of distinguishing between bacterial and rheumatic pneumonia, but also because the pneumonic lungs are vulnerable to secondary bacterial invasion. Levy[56] in 1948 reported 6 cases, 2 treated with sulfadiazine without response, and 2 treated with penicillin without improvement. He noted no response in 5 cases with salicylate therapy. Benadryl was tried in one case without benefit. The conclusions were that there was no specific therapy for rheumatic pneumonitis. Neubuerger[71] in 1944, and Nittono and Hoshiyama[72] in 1940 reported no success with sulfonamide drugs in rheumatic pneumonia. Seldin[90] in 1947 had no favorable response to penicillin given intravenously in this condition.

Benoist[5] in 1900 said the response to salicylates in rheumatic pneumonia was prompt and might be diagnostic. Fischel[26] in 1952 stated that pleuritis once occurred during salicylate therapy in one of their cases, but they stated that salicylates may affect rheumatic inflammation of the "extra-articular serosal membranes." Gamna[30] wrote of clinical cases which responded to salicylates. Goyena[35] wrote that the response of the pulmonary manifestations was prompt.

On the other hand, Caussade and Tordieu[12] said that the salicylates had no effect on the pulmonary or pleural lesions. Grenet[36] stated that the salicylates were not effective in pulmonary or pleural manifestations. Myers and Ferris[69] stated that the salicylates not only did not help, but that the pleural manifestations interfered with the usual salutary effect they had on joint symptoms. Naish[70] wrote that salicylates did little except keep the fever down; Reimann[84] that the salicylates may relieve the discomfort in rheumatic pneumonia. Seldin, Kaplan, and Bunting[90] obtained no response to salicylates, digitalis, or intravenous penicillin. Sokolow and Snell[92] described a patient who had pneumonia, pericarditis, and pleurisy, treated with salicylates, in whom the fever persisted for 13 days of treatment.

Stewart[94] wrote that salicylates were effective against pericardial effusion, but did not mention pneumonia.

Reimann,[84] writing in 1954, stated that rheumatic pneumonia "no doubt will respond to therapy with cortisone and ACTH as other rheumatic manifestations do." The interesting possibilities suggested by these agents have been and are being investigated, but there are few published accounts of their use in rheumatic pneumonia. Chancey[13] in 1953 reported 2 cases of rheumatic pneumonia treated with intravenous ACTH which he considered lifesaving. In each case, however, the pneumonitis developed while the patients were receiving 300 mg. of cortisone daily. In neither case was there residual cardiac damage. The prompt clearing and the lack of cardiac findings make the diagnosis of rheumatic pneumonia open to some question. Shopfner and Seife[91] in 1952 reported a case of rheumatic pneumonia which occurred as a rebound phenomenon after small doses (50 mg. per day) of ACTH were discontinued. Their patient died in a few hours, and rheumatic pneumonia was confirmed at autopsy. Lustock and Kuzma[116] in 1956 also reported on the failure of ACTH in one of the patients in their series.

No other reports of cases treated with these hormones have been found. Dorfman,[21] Massell,[61a, b] Robinson,[86] Fischel,[26] Bunim,[108] Rowe,[109] Wilson,[110] Harris,[111] Markowitz,[112] Houser,[113] Taran,[114] and Barnes[115] have all written on the subject of ACTH and cortisone in rheumatic fever, but did not report cases of pneumonia treated with these agents.

SUMMARY

1. Involvement of the lungs by the rheumatic process has been recognized and described for many years, as far back as the late eighteenth century.

2. There are no reliable figures on the frequency which this manifestation is seen in rheumatic fever. The available data show a range of 2 per cent to as high as 60 per cent.

3. The etiology and pathogenesis are imperfectly understood. The most likely considerations are that: (a) The pneumonia is part of the rheumatic process. (b) The pneumonia is secondary to the cardiac lesion or cardiac failure. (c) Intercurrent infection is

the basis for the pneumonia. (d) The pneumonia is a combination of a and b.

4. The *clinical picture of this syndrome* is not specific, so that the diagnosis is difficult to make ante mortem but it may be suspected. The diagnosis can be made with certainty only by gross post-mortem and microscopic examination of the heart and lungs.

5. Laboratory procedures offer little in establishing a definite diagnosis of rheumatic pneumonitis. The findings by roentgen ray may be suggestive, but not diagnostic. The evidence of pneumonitis is usually a patchy, migratory, and persistent type of infiltration.

6. In considering the differential diagnosis, one must consider active carditis, acute pulmonary edema, bacterial and viral pneumonia, and pulmonary congestion caused by chronic valvar disease.

7. The prognosis is very grave since rheumatic pneumonitis seems to occur in individuals who have associated severe involvement of the heart.

8. The results of treatment are difficult to evaluate because it is difficult to make the diagnosis ante mortem. Little is known about the effect of hormone therapy upon rheumatic pneumonia.

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Comments on Current Literature

CONGENITAL DAMAGE TO THE CENTRAL NERVOUS SYSTEM AS A RESULT OF INTRAUTERINE INFECTION

ONLY within comparatively recent years has fetal infection been recognized as a primary cause of central nervous system disease in the newborn infant, intrauterine infection having been considered of relatively rare occurrence in the past. On the basis of extensive survey studies at the Chicago Lying-in Hospital from 1939 to 1943, Potter and Adair[1] concluded that "infections are not common in this period (early neonatal), and the few which are found consist almost entirely of pneumonia." In one series of 2,000 consecutive fetal or neonatal deaths reported in 1940, Potter[2] found infection other than syphilis in only about 8 per cent. All of these infections were classified as pneumonia on the basis either of gross or of microscopic study. Within the past decade, however, evidence has accumulated which would place intrauterine infection in a more important position as a cause of meningitis or encephalitis in the newly born infant and as a source of changes capable of disturbing the normal course of central nervous system development.

Among the types of fetal infection reported, toxoplasmosis and some infections of viral etiology have been prominent. Toxoplasmosis, a protozoan infection, produces severe damage in the central nervous system of the human fetus, yet the mother may show no overt signs of disease. The same situation may obtain in viral infections which are subclinical or completely silent. With increasing knowledge concerning the behavior of viruses and their tendency toward systemic spread, possible placental transfer of such agents assumes a new significance. As early as 1943, Medovy[3] cited two examples of encephalitis occurring in newborn infants during a sizable outbreak (509 recognized cases) of Western equine encephalomyelitis in Manitoba. Onset of illness in these two newborn infants was on the third and fourth days of life, respectively, while they were still in the maternity hospital nursery. In each instance the mother had experienced a recent febrile illness and showed laboratory evidence of Western equine encephalomyelitis. Both infants developed significant antibody titers against the Western equine virus. Subsequently both showed evidence of residual damage and were admitted to the Children's Hospital at Winnipeg for evaluation because of spasticity, slow development, and apparent mental retardation. Two cases of Western equine encephalomyelitis in newborn infants were encountered in recent epidemics in the western part of the United States (1956-1957). Moderately severe clinical manifestations were apparent soon after birth, and the infection was considered congenital. At the present time these infants are being followed closely for the development of sequelae.

Congenital damage to the central nervous system in animals as a result of virus infection in the mother is well recognized by husbandmen and veterinarians, both in natural infections and in immunization procedures. Immunization of pregnant swine with living attenuated hog cholera vaccine is contraindicated for this reason.[4] Hog cholera virus attenuated by rabbit passage until it has lost all capacity to induce significant symptoms in swine, constitutes an excellent immunizing agent which has been used extensively in this field. However, when sows are inoculated in the first thirty days of pregnancy, gross fetal damage results. One-third to one-half the young may be stillborn, and the remainder show marked congenital malformations. Active virus can be recovered readily from fetal spleen and from other tissues. Similar damage to the fetus has been reported following the vaccination of sheep against catarrhal fever (blue tongue virus) within the period covering the first two months of pregnancy. Stillbirths studied for pathogenesis showed brain malformation and a condition resembling internal hydrocephalus. Surviving young may be retarded in growth and development, may be blind or dumb.[5] Similarly, during epizootics of Japanese B encephalitis in swine, large numbers of stillbirths and abnormal offspring have been recorded.[6] Serum surveys among swine in one such epidemic area suggested a high incidence of inapparent infection with the virus of Japanese B encephalitis. Pregnant females, apparently normal, gave birth to their young at or near the expected date of delivery. In some instances all the young in the litter were dead; in other instances, live, dead, and moribund piglets were observed in the same litter. Those alive were observed to be weak and unable to stand or to nurse. Some young, which appeared normal at birth, later developed signs of central nervous system involvement. Necropsy findings on a number of the latter group included encephalomalacia, hydranencephaly, and changes in the cerebral blood vessels. The virus of Japanese B encephalitis was isolated from brain tissue in the case of three of these piglets.

An interesting and informative review by Potter,[7] which concerns placental transfer of viruses in human subjects, appeared in the *American Journal of Obstetrics and Gynecology* for September, 1957. Presented at a meeting of the Chicago Gynecological Society, this report summarizes the present-day position with respect to placental transmission and has special reference to the "intrauterine origin of cytomegalic inclusion body disease." The author stresses the fact that human salivary gland virus, rarely responsible for overt illness in the mother, may cause severe damage or fatal disease when transferred placentally to the fetus. "Whenever a child is born with symptoms of severe erythroblastosis, the possibility that these may be caused by salivary gland virus, and not by maternal isoimmunization must be considered. This is especially true if the mother is Rh positive." The pathogenesis of the disease varies according to age at the time of infection. When manifestations are noted at birth, infection has probably occurred early in intrauterine life; typical findings of the disease at birth include splenomegaly and hepatomegaly, erythroblastemia and anemia. Jaundice appears within a few hours after birth, blood destruction with compensatory erythropoiesis being marked in this congenital form. At necropsy, extensive ectopic erythropoiesis is apparent, and in many viscera greatly enlarged cells are seen which contain intranuclear and intracytoplasmic inclusions. When the disease has been acquired in utero, these cytomegalic inclusions are more prominent in the kidney than in other organs. Potter points out that both in newborn infants and in older infants and children, examination of the urinary sediment is rewarding as a diagnostic procedure, since typical desquamated renal tubule cells containing intranuclear, or intracytoplasmic inclusions, or both, will be seen in the urine. If the infection is acquired in infancy, symptoms referable to the respiratory tract or the intestinal tract are prominent, with inclusion bodies found most abundantly in the lungs. While in older children and adults the infection seems to be localized in the salivary glands, which show numerous inclusions, actually the virus is widespread in the body—in the liver, kidney, and other organs.

Potter refers to the work of Smith[8] on salivary gland disease: recognition of the disease, its pathogenesis in mice, propagation of the viruses of mouse and human salivary gland disease in tissue culture. "With the report by Margaret Smith in April, 1956, of the successful propagation of human salivary gland virus in tissue culture, the last doubt was dispelled that these inclusions in the human are caused by a virus which, like salivary gland viruses found in other animals, is species specific."[7] Potter refers also to the work of Weller and his associates[9] concerning the isolation of strains of salivary gland virus from living children with signs and symptoms of cytomegalic inclusion disease: isolation of virus in one patient from liver biopsy tissue taken at the age of 3 months; in a second patient from liver biopsy tissue and from urine specimens taken on three occasions. In a third child who had been ill since birth, typical cytomegalic cells with inclusions had been observed repeatedly in the urinary sediment, and the virus was isolated from urine for a period of ninety-one days. This persistent viruria may be of considerable significance.[9] When cerebral calcification is present in inclusion body disease, the condition must be differentiated from congenital toxoplasmosis. Calcification in inclusion body disease, however, occurs largely in the subependymal regions of the lateral ventricles, associated with dilatation of the ventricles and poor development of the convolutions. In toxoplasmosis, the calcification shows a more variable distribution and is of later appearance. In both types of infection destructive action of the organisms may be restricted to a limited area of the brain, the electroencephalogram may be entirely normal, and the objective signs of retardation transient and difficult to evaluate.[10] While the salivary gland virus does have a definite predilection for brain tissue, the degree of invasion and destruction varies, with resultant variability in the sequelae. Some fetuses seem to be more susceptible than others; some escape infection entirely. Potter points out that subsequent birth of a normal infant is possible, either because of fetal resistance or because the virus no longer passes the placental barrier.

While bacterial meningitis with attendant central nervous system damage in early neonatal life does not appear to be of common occurrence, a number of instances have been recorded in which infection of the meninges was thought to be of antenatal origin. These recorded cases include intrauterine and neonatal otitis with otitic meningitis,[11] antepartum gas bacillus infection with loss of the fetus in a mother with septicemia,[12] transplacental infection with hemolytic streptococcus,[13] intrauterine infection with *Leptospira icterohaemorrhagicae*,[14] etc. An interesting case was described in 1951 by Crosby, Mosberg, and Smith[15] under the title, "Intrauterine Meningitis as a Cause of Hydrocephalus." This case was that of a female infant who was admitted to the hospital at 3 days of age because of an enlarged head evident even before birth. The enlarged head had been suspected during the seventh month of pregnancy, and, at the time of the eighth-month routine examination, x-ray studies verified this impression of hydrocephalus. After six weeks of unsatisfactory treatment, surgical intervention was attempted. Exploration of the meninges showed the presence of a yellow organizing exudate from which a pure culture of *Staphylococcus aureus hemolyticus* was obtained. Investigation into the mother's history revealed intermittent upper respiratory infections throughout the entire pregnancy. During the third month, impacted molar teeth had been removed with prompt healing of the sockets and no apparent ill effects. There was no question in this case of premature rupture of the membranes, and the authors concluded that the "probable mode of infection in this infant was by a transient blood stream infection in the mother with transplacental transmission . . . between the sixth and seventh months." The child was followed closely for about one year when the head and chest both measured 52 cm. in circumference; the anterior fontanel was still open at this time, and moderately tense; the coronal suture was readily palpable and slightly separated. Follow-up beyond one year was not possible.

Fungus infection of the vagina during pregnancy is a frequent complication. Usually there is no untoward effect on the course of the pregnancy or on the development of the fetus. Under certain circumstances, however, severe damage of the developing central nervous system is possible. Three newborn infants with diffuse fungus infection *(Cryptococcus neoformans)* were described in 1948 by Neuhauser and Tucker.[16] Each of these patients showed clinical evidence of hydrocephalus and, on roentgenographic examination, "confluent calcification of the severely degenerated brain." The infections were "evidently acquired in utero, during delivery, or very early in the neonatal period. The damage produced by the fungus was severe, and in these three patients fatal within the first few weeks after birth."[16] Two recent case reports, one in the British and one in the American literature, likewise call attention to the potential fetal hazards associated with fungus infection in the mother. The April, 1957, issue of the *Archives of Disease in Childhood* carried a brief but careful study by Burry[17] of Christ Church, New Zealand, reporting a case of hydrocephalus associated with intrauterine fungal infection. The infant, a male with birth weight of 7½ pounds, was born at term after a "short forceful labor" of two hours' duration. Conception had followed closely after dilatation and curettage and tubal insufflation, carried out because of apparent infertility. The infant was slow to breathe and cry, but responded well to oxygen and incubation. Soon after birth it was noted that the child's sucking and swallowing reflexes were poor, and for the first fortnight tube feeding was required. Twitching of the eyelids and face began on the third day of life; on the fifth day, undue separation of the skull sutures was apparent, and the diagnosis of hydrocephalus was suggested. Under constant care this child survived for thirty-seven days. Postmortem examination revealed gross hydrocephalus involving the lateral and third ventricles; the cerebral hemispheres were tense and distended with marked flattening of the sulci; a pale organized exudate covered the occipital poles. Sections from the lining of the lateral ventricles showed loss of much of the ependymal layer, the cells of remaining portions being flattened to cuboidal form. "Beneath a layer of glial scarring, and at some points penetrating more deeply into the brain substance, were irregular masses of partly calcified necrotic material and structures identifiable by P.A.S. stains as hyphae and spores of a fungus." Unfortunately no cultures were attempted; however, the presence of septate pseudomycelia and small spores suggested *Candida albicans* as the most likely pathogen. The grave condition of this infant at birth and the subsequent pathologic findings led the author to the conclusion that this infection was intrauterine in origin. The second case report, which appeared in the *American Journal of Obstetrics and Gynecology* for January, 1958, describes *Candida albicans* infection of the amniotic sac. This report is believed by the authors, Benirschke and Raphael,[18] to be the first recorded instance of *Candida albicans* infection of the umbilical cord. The mother, gravida ii, para i, was in the second month of pregnancy when first seen by her obstetrician. She was complaining of vaginal irritation for which she had been employing self-medication. Following proper treatment this condition improved, and the months following were uneventful. In the sixth month, however, premature labor began, and a female anencephalic infant was delivered by breech presentation. This child lived for about forty minutes after birth; autopsy was not performed. The placenta, cord, and membranes were studied in detail; the fetal surface of the placenta showed severe chorioamnionitis. The amniotic epithelium had degenerated almost completely, and the underlying connective tissue of the amnion and chorion was infiltrated with acute inflammatory cells. Walls of the fetal blood vessels were damaged, and sections of the umbilical cord revealed acute inflammatory cells (fetal) in the walls of the umbilical vessels and in the cord substance. Large colonies of fungus growth were present on the surface of the cord. Widespread distribution of the fungus was apparent on staining with P.A.S. stain. *From the surface of the cord* and amnion *Candida albicans* was isolated in pure culture. Since there was no history of premature rupture of the membranes, the authors suggest that an early subclinical rupture of the membranes with subsequent sealing of the rupture site might have occurred during active moniliasis in the mother. The condition of the child at birth and the extent of involvement of the cord and membranes suggested that the infection was of considerable duration.

Such infectious agents transferred from the mother to the fetus may bring about their effects either directly on the fetal tissues or indirectly by altering the general fetal milieu. Some of these agents seem to have an affinity for the blood vessels, particularly the arteries of the cerebral circulation. In developing chick embryos artificial partial occlusion of major cerebral vessels has been shown to result in disturbance of differentiative processes and in retardation of the subsequent development of the brain. The association of vascular anomalies with anencephaly in the human fetus, in the absence of known infection, is being studied currently by pathologists.[19] Composite information accumulating from all sources will help to further a basic understanding of the disturbances in fetal life which interfere with the normal course of central nervous system development.

Russell J. Blattner

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News and Notes

The National Association for the Prevention of Tuberculosis will hold a Commonwealth Chest Conference in London, July 1 to 4. Representatives from thirty-five different countries are expected to attend. Further information as to the program, etc., may be obtained from the National Association, Tavistock House North, Tavistock Square, London, W.C. 1, England.

Among the twenty-five scholars in medical science recently appointed by the **Markle Foundation,** two in the field of pediatrics are included: Donough O'Brien, of the University of Colorado School of Medicine; and Ned W. Smull, instructor at the University of Kansas School of Medicine in Kansas City.

The **Cook County Graduate School of Medicine** announces a two-week intensive course in Neuromuscular Diseases of Children with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the period of July 7 to 18. This is an intensive didactic and clinical course designed for pediatricians, orthopedists, neurologists, psychiatrists, and physiatrists interested in the care and treatment of children with neuromuscular handicaps. Emphasis will be placed on the practical clinical aspects of treatment and rehabilitation procedures. The course will include trips to demonstration clinics and treatment centers. Registration is limited. For further information, write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood Street, Chicago, Ill.

The Tenth Annual Summer Clinics of The Children's Hospital in Denver, Colo., will be held June 18, 19, and 20, 1958. Designed for all physicians concerned with the care of infants and children, the course will present recent advances in medical knowledge appropriate to practice and will emphasize early recognition of disease and common problems in the management of children's diseases, and will outline successful programs of therapy.

Guest faculty this year will be Dr. Lee Forrest Hill, Chief of Staff, Raymond Blank Memorial Hospital, Des Moines; Dr. Meyer A. Perlstein, Professor of Pediatrics, Cook County Hospital, Chicago; and Dr. William B. Kiesewetter, Surgeon in Chief, Children's Hospital of Pittsburgh.

Further information can be secured by writing the Chairman, Summer Clinics Committee, Children's Hospital, Denver 18, Colo.

Childrens Hospital, Columbus, Ohio, affiliated with the Ohio State University College of Medicine, offers a one-year residency in pediatric allergy to candidates with two years accredited residency in pediatrics. Address correspondence to John H. Mitchell, M.D., Division of Allergy, Ohio State University, Columbus, Ohio.

The Editors of *Modern Medical Monographs,* a quarterly publication, announce an award for the best unpublished manuscript for a short book on a clinical subject in the field of internal medicine. The purpose of this award, which will be known as the **Modern Medical Monograph Award,** is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing. The winner of this competition will receive five hundred dollars. In addition, the winning monograph, if found suitable, will be published as a book in the series *Modern Medical*

Monographs. The generosity and cooperation of Dr. Henry M. Stratton, President of Grune & Stratton, Inc., publishers of the series, have made this award possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monographs.*

The rules are as follows:

1. The author (or authors) must be a graduate physician, less than 40 years of age. Single authorship is preferred, but two co-authors will be acceptable. The name of the medical school from which the author graduated and his date of graduation should be stated.

2. Manuscripts should be submitted in duplicate (original and one copy) by registered mail, postmarked *no later than Oct. 1, 1958,* to Richard H. Orr, M.D., 37 East 67th St., New York 21, N. Y.

3. The manuscript, including the bibliography, must consist of between 115 and 200 double-spaced typewritten pages with ample margins and not more than 40 illustrations (figures or photographs). For each illustration used, the allowable upper limit of typewritten manuscript pages should be reduced by one.

4. Fishbein's book, *Medical Writing* (third edition), should be followed in preparation of the manuscript, use of abbreviations, and bibliographic form.

Richard H. Orr, M.D.	Irving S. Wright, M.D.
Consulting Editor	Editor-in-Chief

The **University of Nebraska College of Medicine** offers a postgraduate course, Allergy Conference, May 8 and 9, 1958. May 8 will be given to Pediatric Allergy, followed in the evening by a dinner with the Nebraska Pediatric Society, at which there will be a panel discussion on the "Use and Abuse of Drugs in the Treatment of Allergy." Details may be obtained from Dr. Lawrence A. Cappiello, Supervisor of Medical Extension, University of Nebraska Medical School, Omaha 5, Neb.

A **Postgraduate Seminar in Pediatrics** will be conducted by the combined faculties of the Georgetown and George Washington Departments of Pediatrics at the Children's Hospital of Washington, D. C., on May 22, 23, and 24, 1958. The program will be given by members of the two teaching institutions and guests from The National Institutes of Health, The Walter Reed Army Medical Center, and The Bethesda Naval Hospital.

Further information may be obtained from The Director of Medical Education, Children's Hospital of Washington, D. C., 2125 Thirteenth Street, N.W., Washington 9, D. C.

The **XI Polish Pediatric Congress** will be held on June 6, 7, and 8, 1958, in Wroclaw. The main problems of the Congress are: (1) meningitis in children (excluding tuberculous meningitis), (2) staphylococcal infections in children.

Books

Sins of Their Fathers. Marjorie Rittwagen, M.D., Boston, 1958, Houghton Mifflin Co., 264 pages. Price $3.50.

Juvenile delinquency—the theme of this book—is a subject of much concern. Seemingly a rapid increase is taking place, and our newspapers in recent months have been filled with lurid accounts of "teenage" gangsterism and of delinquents involved in murder, rape, robbery, and vandalism. It is a national problem not confined to any one city or section. While fundamentally a social, and to some extent a psychiatric, problem, it is a matter of interest to the pediatrician who is so deeply concerned with all aspects of the welfare of children. It is for this reason that this book by Dr. Rittwagen, Staff Psychiatrist to the Court of Domestic Relations of the City of New York, is of unusual interest. It covers the subject in a broad way, and her experiences with and observation of delinquent children over a five-year period is presented in an interesting and readable way. The title of the book indicates the author's general conclusions as to the chief or fundamental causes of juvenile delinquency. The delinquent child comes usually from a home that is broken or unwholesome, as a result of psychotic, alcoholic, immoral, or mentally retarded parents. As a result of the home situation, the child is deserted or neglected or abused, and deprived of the normal emotional needs of the young child. There are many factors involved which are often combined as regards the specific child. One of these is the density of the child population in an area in relation to the schools and recreational facilities available. In this connection is the interesting observation that the juvenile delinquency rate is increasing in the modern new housing projects being built in many cities to replace the run-down slum areas. The author's approach is by a limited case history record upon which the general discussion of the particular point or subject is developed, and in this way the many facets of the problem are skillfully presented. Much of the discussion is concerned with the work of the governmental and private agencies that are trying to cope with the problem, such as the courts and detention homes, the hospital and psychiatric clinics, the welfare and religious organizations. These are woefully inadequate compared with the magnitude of the problem.

It is a sordid and distressing picture. While fully agreeing with the author that what is needed is adequate personnel and increased facilities of a number of kinds to meet the present urgent problem, increase in the psychiatric facilities, for example, will not reach the basic problem of removing or correcting the causes of juvenile delinquency. The many-sided factors or influences that lead to juvenile delinquency are well stated in a sentence by the author: "The delinquents I've seen are the products, then, of their genetic inheritance, their parents' influence, their neighborhood, their schools, their church, their time." The book gives an excellent picture of the juvenile delinquent and his personal and community problems. The book is very well written.

B. S. V.

Reaching Delinquents Through Reading. Melvin Roman, Ph.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 125 pages. Price $4.50.

It is generally accepted that a close relationship exists between personality difficulties and reading disabilities. Several studies have shown that about 85 per cent of juvenile delinquents have reading disabilities compared with 10 per cent of all children of school age. Dr. Roman, former Director of Group Psychotherapy of the New York City Court of Domestic Relations, in this monograph discusses the problem and therapy. He considers what is called "Tutorial Group Therapy" as the method producing the best results. The book is of interest to those working with the juvenile delinquent rather than of general interest.

Urine and the Urinary Sediment. Second Edition. Richard Lippman, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 140 pages. Price $8.50.

This book contains an excellent section on the significance and source of protein and the formed elements of the urine. There are 92 colored photographs showing the various types of casts, red and white blood cells, epithelial cells, crystals, yeast, fat, bacteria, etc.

Another section deals with urine and its sediment in various diseases. There is also a brief clinical classification of these diseases.

A third section deals with general considerations of urine (volume, appearance, color, odor, pH) and technical descriptions of timed urine collections, methods of qualitative and quantitative examinations, and descriptions for staining sediment. This book is easily read and contains much valuable information. The excellent colored photographs should make it extremely valuable to the relatively inexperienced observer.

H. W.

A Parents' Guide to Children's Illnesses. John Henderson, M.D., New York, 1957, Duell, Sloan & Pearce, Inc., 398 pages. Price $4.75.

This is another of the many books on children's diseases written for parents. It is the experience of many pediatricians that such books often do more harm than good, in line with the sound adage that a little learning is a dangerous thing. Parental diagnosis can be very dangerous to the child. Dr. Henderson's text, in the opinion of the reviewer, goes into far too many details and would be confusing rather than helpful to most parents. There are eight pages of rather poor colored plates containing twenty-six pictures of rashes and other lesions. Some are rather silly to include in a book for parents, such as pustular lesions on an ankle and part of a leg labeled "smallpox." There are several better books available for parents on children's illnesses which the reviewer would recommend if the necessity arose.

The Infantile Cerebral Palsies. Written by the Little Committee for the Study of the Infantile Cerebral Palsies (Drs. W. R. F. Collis, William Dunham, L. T. Hilliard, David Lawson, and Mrs. Eirene Collis. Foreword by Sir Francis Walshe), Springfield, Ill., 1957, Charles C Thomas, Publisher, 100 pages. Price $3.00.

This short monograph is a very worthwhile addition to the voluminous literature on the subject of the cerebral palsies. The discussion goes back to Little's descriptions and writings in 1853, and emphasis is placed on the "new" approach to cerebral palsy in recent years being simply a return to the views expressed by Little over 100 years ago. The text takes up the diagnosis, types, and management of the condition. This is followed by a discussion of the organization of cerebral palsy services. All members of the Little Committee have been working in the field of cerebral palsy, and their contribution is well worth while. It is a well-written and interesting presentation of the subject. Recommended.

Metabolic Aspects of Transport Across Cell Membranes. Q. R. Murphy, Editor, Madison, Wisconsin, 1957, The University of Wisconsin Press, 379 pages. Price $7.50.

This book includes papers and discussions of a symposium held at the University of Wisconsin under the sponsorship of the University Medical School. With the purpose of summarizing and correlating the large amount of information available on membrane transport, the symposium emphasized problems involving skin, nerve, muscle, gastric and intestinal mucosa, and the kidney. Discussions of fluid exchange and the effect of metabolic derangements on ion exchange in the whole organism were included, and some attention was given to possible correlations of clinical problems and basic information.

A. F. H.

Stedman's Medical Dictionary, ed. 19. Edited by Norman B. Taylor, M.D., F.R.C.S.(Edin.), M.R.C.S.(Lond.), Baltimore, 1957, Williams & Wilkins Co., 1656 pages. Price $12.50.

A new revised edition of Stedman's dictionary. Several thousand new words and terms have been included which have come into use since the last edition four years ago. The names of pharmaceutical preparations have been changed from Latin to English in conformity with the changes in the American and British pharmacopeias.

Aids to Diagnosis and Treatment of Diseases of Children, ed. 10, F. M. B. Allen, M.D., F.R.C.P.(Lond.), Baltimore, 1957, Williams & Wilkins Co., 302 pages. Price 10s. 6d.

A small pocket-sized book in the Students' Aids Series published in England. The pediatric text first appeared in 1893, and, since 1927, has been written by Dr. Allen of the Royal Belfast Hospital for Sick Children. It is more of a miniature text than a synopsis, and from the number of editions has evidently been popular with British medical students. Good of its kind.

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Deafness, Mutism and Mental Deficiency in Children. Louis Minski, M.D., New York, 1957, Philosophical Library, Inc., 82 pages. Price $3.75.

In this book Dr. Minski gives an excellent textbook presentation of the subject of deafness and mutism in children. He stresses the importance of differentiating between mentally defective and deaf children and presents a lucid exposition of the techniques of assessing deafness-audiometry, electroencephalography, and psychologic testing.

Manual of Pediatric Physical Diagnosis. Lewis A. Barness, M.D., Chicago, 1957, The Year Book Publishers, Inc., 195 pages. Price $4.00.

This excellent manual is the outgrowth of mimeographed notes for second-year medical students at the University of Pennsylvania Medical School started several years ago. Its purpose is to acquaint the student with the methods of physical diagnosis used in the examination of the infant and child. Perhaps the chief criticism is that it may be too complete and elaborate for the medical student.

Microtechniques of Clinical Chemistry for the Routine Laboratory. Samuel Natelson, Springfield, Ill., 1957, Charles C Thomas, 484 pages. Price $11.00.

This book defines the need for the terminology of microanalysis. It then proceeds to describe the equipment needed and the proper technique required for sampling and handling of samples. The majority of its chapters are directed to the microdetermination of almost any substance that a modern laboratory might be expected to run. Measurements are for the most part made with standard laboratory equipment. This book also contains a good bibliography as well as a list of manufacturers of micro equipment.

A. F. H.

The Year Book of Pediatrics. Edited by Sydney S. Gellis, M.D., Chicago, 1957, The Year Book Publishers, Inc., 469 pages. Price $7.50.

The 1957 year book, as usual, contains excellent abstracts of pediatric articles appearing through May, 1957. Many are followed by editorial comment. Dr. Gellis maintains the high standards set by Dr. Poncher a few years ago.

Fun Comes First for Blind Slow-Learners. Mildred B. Huffman, B.E., M.A., Springfield, Ill., 1957, Charles C Thomas, Publisher, 157 pages. Price $5.00.

Mrs. Huffman is a teacher at the California School for the Blind and has the position of teaching retarded blind children, a task most of us would consider hopeless. In this monograph she tells of the methods she has developed and used in her work and the achievements of the children under the program.

Editor's Column

THE CANNED BABY FOOD WAR

FOR many years, since the canned baby food business was started by Clapp in the early twenties, we have watched the growth of the industry and its ups and downs, as it has been of interest and importance to pediatricians. Much of the advertising, particularly in the early days, has been directed toward gaining their support.

The canned infant food products filled a need, and have played a definite part in improving infant nutrition and in making life easier and happier for hundreds of thousands of mothers. The growth of the industry in recent years has been phenomenal. According to a report in *Barron's* of last February 10, while the increase in the birth rate, 1947 through 1956, rose about 10.5 per cent, the tonnage of canned infant foods shipped during this period increased by nearly 45 per cent. The estimated annual dollar income from sales during this period increased from around $109 million to over $300 million, or nearly 60 per cent.

Clapp, the first company in the field, was started in the kitchen of a home, and its ownership has changed hands several times. It now is a division of Duffy-Mott, engaged chiefly in apple products, and if memory serves correctly, was at one time owned by American Home Products. Clapp started by retailing through the drug stores, but Gerber, who entered the business later in the twenties as a side venture of a canning factory, used grocery stores as an outlet and set the pattern in use today. Gerber today holds the number one position in the industry, with around ninety canned items, and is said to account for roughly one-third of the total sales volume. Next come Heinz and the Beech-Nut Life Savers companies. The annual infant food business of the latter is estimated around $50 million. Other companies are the Clapp, and Libby. Mead Johnson is reported as acquiring the Bib Company. To these must be added the meat packers such as Swift and Armour, who process canned meats for infants. While prohibited from canning vegetables, they supply the meat for the meat-vegetable combinations. Armour is said to supply Gerber, and both companies market the Gerber products containing meat. A similar arrangement between Beech-Nut and Swift is reported as having been switched to Hormel.

Naturally intense competition has developed with so many companies engaged in a struggle for the same market, and percentagewise the profits from sales has fallen, although the earnings are substantial. Some of the companies have centered on the use of glass containers, and others on less expensive metal. There has been a definite shift toward glass in recent years, which was the original form of the container used by Clapp. There has been a geographical element involved in the distribution and use of the products of the different companies, with the sales of one company leading in one section of the country and another leading in some other section.

While the products of the canned food industry have played a part in what might be described as the "harmony" of life and living, in that they have led to an improvement in the well-being of infants, and hence to happiness and peace in the home, there is considerable "disharmony" among the companies in the industry. While this in no way involves the pediatrician, who will continue to use the useful products brought out by the rival companies, the rows that have developed are of interest to him as he is very much involved in the use of the various products.

Financial papers have recently reported that suits have been brought by the Gerber and by the Heinz companies against Beech-Nut, charging unfair competition in California, with violations of the Sherman, Clayton, and other Acts of Congress. Damage suits aggregating $26 million have been filed. Many charges are involved: price differentials, false advertising, unfair promotions, rebates, etc. One of the claims reported as a basis for one of the suits is that Beech-Nut representatives bought out the entire product of one of the companies in some supermarkets, so that only their own products would be left on the shelves for customers. Naturally there are denials and counterclaims.

It usually takes many months and even years before such suits come to trial. We have no opinion as to the right or wrong of the claims made by the companies involved. The products of the companies, however, have been an important contribution to infant feeding and nutrition and are designed for use as advised and directed by the pediatricians. For this reason the pediatricians have an interest (not financial) in the companies, and the outcome of this internecine warfare will be closely followed by those of us with seats on the sidelines.

Under the circumstances it might be a wise precaution if the booths of the warring companies were widely separated in setting up the commercial exhibits at pediatric meetings, so that as innocent bystanders we will not be hurt if the cans begin to fly.

MEDICAL SCHOOLS AND MEDICAL STUDENTS

AT PRESENT there are 83 *approved* medical schools in the United States, of which 79 have 4-year programs. Two others, Florida and Seaton Hall, will become eligible in 1960 when their first classes are graduated, and a 4-year school at the University of Kentucky is scheduled to open in 1959. In the 1956-1957 school year there were 29,003 medical students enrolled in the 83 schools, and, in addition, 127 attending the two schools mentioned above. Ten years previously, 1946-1947, the number of medical students enrolled was 23,900. Thus an increase of 21 per cent in the number of students has taken place in the ten years.

The rush for higher education which led to so many seeking admission to the medical schools following World War II has eased. For the entering class in 1949 there were 3.5 applicants for each place available. By 1955 this had dropped to 1.9. The situation, however, is beginning to reverse itself, and medical educators believe that by the mid-sixties there will be a return to the 1949 situation. The average applicant continues to apply for admission to several schools. In 1956 there were close to 16,000 applicants who filed nearly 60,000 applications or 3.8 per applicant. This varies little from the figure for a number of past years.

The teaching responsibilities of the medical school faculties are not limited to the teaching of the 29,000 medical students. In 1956-1957 the schools carried teaching responsibilities to 63,000 other students, as interns, residents, fellows, postgraduates, and advanced students, and to dental, pharmacological, and nursing students.

The demand for more doctors will increase in the years to come with a rapidly increasing population and with so many in the old age group. The ratio of 133 doctors to every 100,000 of population in the United States has changed little in recent years. The demand for more doctors for services of a governmental nature, and for industry, is steadily increasing. The Association of American Medical Colleges in 1956 recommended that the increase in the number of physicians needed should be met by increasing the number of medical schools. In 1957 the Association proposed that the universities should be encouraged to develop programs that would offer the first two years of the medical course. A survey has shown that the present 4-year schools have facilities to train between 300 and 400 additional third and fourth year students. This proposal has been concurred in by the Council of Medical Education of the American Medical Association.

One of the common misstatements, not infrequently heard, is that an applicant for admission to a medical school to be accepted must have had a college "A" grade scholastic average. The actual percentage of students admitted to the entering class in 1956 by college grades was as follows: "A," 16.1 per cent; "B," 69.9 per cent; "C," 14 per cent.

Along with everything else the cost of a medical education is steadily rising, bringing a very disturbing financial factor into the determination of who will be the doctors of the future. Tuition fees in 1956-1957 averaged $720 for resident students and $918 for nonresidents, as compared with $684 and $857 for 1955-1956. The difference between resident and nonresident involves the state-supported schools.

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GLYCOGEN STORAGE DISEASE OF THE HEART

CLINICAL OBSERVATIONS IN FIVE INFANTS

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BECAUSE glycogen storage disease of the heart is a rare disease, the clinical data accumulated from five infants in whom this diagnosis was confirmed at autopsy seems worthy of presentation. In recent reports,[1, 2, 3] the similarity in clinical manifestations among infants with glycogen storage disease of the heart and amyotonia congenita has been stressed. It is our purpose to emphasize this aspect of the clinical picture since the generalized skeletal muscle involvement rather than the cardiac manifestations *dominated the clinical course of our* five patients.

The rarity of glycogen storage disease of the heart is well documented. In 1950, di Sant Agnese, Andersen, Mason, and Bauman[4] accepted only fourteen cases from the world literature, acknowledging the probable existence of others in which the diagnosis was not conclusively proved. In 1954, Rossi[5] estimated that less than forty cases had been reported to that date. The familial nature of glycogen storage disease of the heart is recognized.[6] A recessive and perhaps sex-linked mechanism of transmission has been suggested.[7] The involvement of multiple siblings in a single family has been reported.[8, 9] Consanguinity has been a finding in several families.

The existence of two main varieties of glycogen storage disease has been described on clinical grounds for many years; namely, the hepatic form originally described by von Gierke in which the liver and kidney are the primary sites of glycogen deposition, and the nonhepatic or cardiac form in which *the myocardium and skeletal* muscles are primarily involved. The studies of Cori[10] have demonstrated a chemical difference between these two entities. Von Gierke's disease, or glycogen storage disease of the liver, is marked by hepatomegaly, renal enlargement, and retarded somatic growth. Hypoglycemia, ketosis, and hyperlipemia can usually be demonstrated together with a diminished response to epinephrine administration. Cori has shown that the glycogen structure in these patients is essentially normal, but that a definite decrease in the *amount of the enzyme*, glucose-6-phosphatase, is present. This enzyme is

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responsible for splitting off phosphate from the glucose molecule and thus permitting its passage into the circulation and delivery to the tissues. A deficiency of this enzyme would likewise impair glycogenolysis. The chief product of glycogen breakdown is glucose-1-phosphate which is then converted to glucose-6-phosphate. Impaired breakdown of the latter component, due to the enzyme deficiency, leads to its accumulation and slowing of the reversible reactions leading from glycogen to glucose.

In contrast to von Gierke's disease, glycogen storage disease of the heart and skeletal muscles is not associated primarily with hepatomegaly and evidence of impaired carbohydrate metabolism. In this disease, muscle weakness, cardiac enlargement, and enlargement of the tongue have been prominent findings. Structurally normal glycogen is found in the involved organs and the amount of glucose-6-phosphatase is apparently normal. At present, no satisfactory chemical explanation is available for the precise metabolic abnormality present in this type of glycogen storage disease. Cori[10] and Recant[11] have listed two other very rare and unusual clinical varieties of glycogen storage disease in which deficiencies in the enzymes responsible for synthesis or breakdown of the branched structure of the glycogen molecule have been demonstrated. The glycogen in the tissues of affected individuals has been found to be of abnormal structure.

Two clinical reports have recently described patients with a nonhepatic form of glycogen storage disease in which the skeletal muscles have been primarily involved with relatively little deposition of glycogen in the myocardium. In the two patients reported by Krivit and associates[2] profound muscle weakness was present, suggesting initially the diagnosis of amyotonia congenita. A primary muscular dystrophy with deposition of glycogen in skeletal muscle was finally diagnosed in each case; no neurological disease was demonstrable. The deposition of small amounts of glycogen was described in the cardiac specimen in one of these cases and increased cardiac weight was found at autopsy in the other. However, both of the patients demonstrated normal electrocardiographic tracings and normal cardiac silhouettes in roentgenograms taken during life. Similarly, the first case described by Zellweger and co-workers[3] also showed extensive skeletal muscle infiltration with glycogen, but a normal heart size was demonstrated on roentgenographic examinations and a normal electrocardiogram was recorded. It thus appears that the relative degree of skeletal or myocardial involvement can vary over a wide range in the nonhepatic form of glycogen storage disease. Patients may demonstrate primarily skeletal or primarily myocardial involvement, or mixed degrees of involvement. In each of the five patients included in the present study, extensive skeletal as well as cardiac muscle involvement was noted both clinically and pathologically. This combined form of involvement in nonhepatic glycogen storage disease is apparently more common than the primary skeletal muscle variety.

The duration of life in most patients with glycogen storage disease of the heart has varied from a few hours to nine months. In the review of Landing and Bangle,[7] several earlier cases,[12] which were reported to have survived for longer periods of time, were considered by the authors to represent another disease entity. Most patients with this disease have eventually succumbed to the complications of respiratory muscle weakness, presumably caused by the deposition of glycogen in these muscles. Relatively few have been reported to have died in a state of congestive failure. No form of treatment has altered the uniformly fatal outcome.

CLINICAL OBSERVATIONS

Since the clinical and pathologic findings in the five infants included in this report are very similar, the details of only a single case will be reported fully. Pertinent clinical findings in all of the five cases have been summarized in Table I. A typical electrocardiographic tracing is presented in Fig. 1. Representative roentgenograms of the chest are presented in Figs. 2 and 3.

CASE REPORT

L. G., a negro male infant, died at the age of 4½ months, one month following admission to the Children's Hospital of Philadelphia. The chief complaint on admission was cough associated with fever of three days' duration.

Family History.—The immediate family consisted of two healthy parents and an 8-year-old half sister born of the mother's previous marriage. The half sister was reported to have congenital heart disease for which she was operated upon elsewhere. At present she also demonstrates evidence of rheumatic heart disease. The patient was the product of the first pregnancy of his parents; a subsequent male offspring is now living and well at the age of 11 months.

The mother had six siblings, all of whom were living and well except one who suffered an accidental death. The father had ten siblings of whom two died in infancy; the first of these succumbing to pneumonia prior to the father's birth. When the father was 13 years old, another younger sibling was born who demonstrated listlessness and weakness associated with a paucity of spontaneous movements. This infant died suddenly during the course of a feeding at home and aspiration pneumonia was suspected. No hospitalization or post-mortem examination was carried out on either of the father's deceased infant siblings.

History of Present Illness.—The patient was born following a 9-month, apparently normal pregnancy with a birth weight of 3,295 grams. No neonatal difficulties were noted. The infant was breast fed for two months and thereafter fed an evaporated milk formula. Supplementary vitamins were administered from birth.

The infant visited the Well-Baby Clinic of the maternity hospital at 1 and 2 months of age. A hernia and hydrocele were detected and plans were made for their future repair. Approximately three days prior to admission a fever associated with cough was noted. Listlessness was also apparent for the first time during this interval. Feedings were taken poorly and some regurgitation occurred. Excessive mucus in the nasopharynx was also noted. A tentative diagnosis of pneumonia was made at the time of admission.

Physical Examination.—Examination on admission revealed a well-nourished and hydrated Negro male infant with mild respiratory distress and a fairly strong cry. Mild retractions of the chest wall were noted with each inspiration. No cyanosis or jaundice was evident. The pulse rate was 136 per minute; respiratory rate 36 per minute; temperature 101.2° F. The body weight was 5,305 grams; the head circumference, 16 inches;

TABLE I. SUMMARY OF CLINICAL FINDINGS IN FIVE INFANTS WITH GLYCOGEN STORAGE DISEASE OF THE HEART AND SKELETAL MUSCLES

CASE NO.	SEX/ COLOR	AGE AT ONSET OF SYMPTOMS	AGE AT HOSPITAL ADMISSION (MO.)	AGE AT DEATH (MO.)	MATERNAL AGE	PATERNAL AGE	BIRTH ORDER	BIRTH WEIGHT (GM.)	FAMILY HISTORY	CHIEF COMPLAINT	CARDIAC MURMUR	CARDIAC ENLARGEMENT
1.	W/M	3 wk.	2	5½	25	28	2nd	3,060	–	Cough, hoarseness, weak cry, poor wgt. gain	+	Moderate
2.	C/M	3 mo.	3½	4½	29	33	1st	3,295	+	Cough, fever	+	Moderate
3.	C/F	Birth	5	7	28	36	4th	1,515	–	Poor development, cough, rapid breathing	+	Moderate
4.	C/F	3 mo.	7	8½	30	50	8th	----	+	Fever, cough, noisy respirations	–	Slight
5.	C/M	2 mo.	3½	5	24	45	5th	3,970	+	Recurrent upper respiratory tract infections	+	Moderate

chest circumference, 15 inches; and body length, 26 inches. Secretions were present in large amounts in the nasopharynx. Over both lung fields coarse breath sounds but no fine râles could be heard. Cardiac enlargement to the left was suspected on percussion. A low-pitched, soft systolic murmur was audible to the left of the mid-sternum; no murmurs were audible posteriorly. No thrills or diastolic murmurs were detected. The liver edge was palpable 2 cm. below the right costal margin. A left hydrocele and left inguinal hernia were present. No obvious neurological manifestations were evident at this time; all reflexes were present and normal.

The diagnostic impression at the time of admission was upper respiratory tract infection, possibly associated with pneumonitis. A roentgenogram of the chest taken at the time of admission showed cardiac enlargement but no evidence of pneumonia or of increased pulmonary vascular markings.

Laboratory Studies.—Hemoglobin level on admission was 9.2 Gm. per cent; little variation occurred during the one-month period of hospitalization. The white cell count on entry was 8,000 and reached a peak of 13,000 approximately one week prior to death. The differential white blood cell count varied, at times showing a predominance of lymphocytes and, on other occasions, a majority of neutrophils. Urinalysis revealed a specific gravity of 1.017 and a pH of 5; no excessive amounts of protein, sugar, or acetone were detected; microscopic examination was negative. A sickling preparation was negative; an old tuberculin skin test in a dilution of 1:1000 was also negative. A blood culture on admission was sterile; cultures of the nasopharynx on multiple occasions revealed no unusual organisms. An electrocardiogram, taken on the day following admission, revealed very high amplitude QRS complexes in all leads with depression of the S-T segments and negative T waves in the limb leads. Roentgenographic examination of the chest was repeated on two occasions and demonstrated no change in the degree of cardiac enlargement. Approximately one week prior to death, atelectasis of the left lower lobe was evident on roentgenographic study.

Blood chemistry studies were as follows: NPN, 36 mg. per cent; cephalin flocculation, negative; thymol turbidity, 1.4 units; serum protein, 5.5 Gm. per cent; serum albumin, 2.4 Gm. per cent; serum globulin, 2.1 Gm. per cent; cholesterol esters, 121 mg. per cent. The serum mucopolysaccharides were found to be normal in total amount and in their electrophoretic pattern. The red blood cell glycogen content was found to be normal, i.e., equivalent to controls. A fasting blood sugar was 79 mg. per cent and one hour after epinephrine was given the blood sugar level rose to 173 mg. per cent. The fasting serum pyruvate was 1.24 mg. per cent, and twenty minutes after the injection of epinephrine the pyruvate level was 2.92 mg. per cent; one hour later it was 2.33 mg. per cent. The response of the blood sugar and pyruvate levels to epinephrine administration was considered normal. The serum levels of sodium, potassium, chloride, and CO_2 were within normal limits.

Hospital Course.—The patient was promptly started on antibiotic therapy but the fever failed to subside. On the fourth hospital day, marked muscular flaccidity and lethargy were noted. Because of this finding associated with cardiac enlargement, a biopsy of the left gastrocnemius muscle was performed. The specimen of muscle showed focal areas in which marked vacuolization of the cytoplasm of the muscle fibers was present. Progressively increasing muscle weakness and flaccidity developed until the infant was unable to suck or swallow; gavage feedings were necessary. Because of some increase in liver size and the presence of respiratory distress, digitalization was attempted.

Gross arrhythmia resulting from digitalis intoxication appeared shortly after one half of the calculated amount of digitalis was administered. This disappeared with a reduction in the dose of digitalis. The difficulties arising from large amounts of tenacious mucoid material in the nasopharynx became progressively greater. Frequent aspirations of the nasopharynx were inadequate and finally a tracheotomy was performed. Death occurred at the age of 4½ months, one month after admission.

Post-mortem examination was carried out promptly. Almost the entire heart, 60 grams of liver, and 20 grams of psoas muscle were frozen within one hour of death. Portions of these tissues were sent in the frozen state to the laboratory of Dr. G. Cori where the following chemical analyses, shown in Table II, were made.

TABLE II

TISSUE	% GLYCOGEN	% GLYCOGEN END-GROUP	% GLYCOGEN SPLIT BY PHOSPHORYLASE	AMYLO 1-6-GLUCOSIDASE IN UNITS/100 MG.
Heart	6.6	6.9	47	120
Psoas	13.0	7.1	42	131
Liver	6.2	7.9	39	—

It was concluded that these tissues contained glycogen of normal structure as well as a normal amount of amylo 1-6-glucosidase, the enzyme responsible for splitting the 1-6-glucosidase linkages which produce the branched structure of the glycogen molecule.

Necropsy Findings.—The heart weighed 46 grams. The systemic and pulmonary venous return was normal as were the great vessels, valves, and septa. The papillary muscles of the left ventricle presented a diffuse gray-pink color which was evident through the transparent endocardium. The left ventricle was hypertrophied and somewhat dilated. Microscopically, the myocardial fibers were increased in size and showed prominent irregular hyperchromic nuclei. The cytoplasm was almost entirely displaced by large vacuoles which stained positively with Best's mucicarmine and periodic acid-Schiff stain.

The liver was enlarged; its surface was smooth and glistening; the edge was sharp. On section, the color of the liver was pale yellow and the architecture appeared normal. Microscopic examination of the liver revealed marked vacuolization; the cell nuclei were in an eccentric position. Special staining techniques demonstrated that the vacuoles contained material with the staining characteristics of glycogen. Skeletal muscle fibers also showed marked vacuolization and apparent loss of cytoplasm. Both lungs were purplish-red and fleshy. There were scattered areas of hemorrhage present. On section there were small collapsed areas and areas of crepitation. Congestion and edema were marked. The trachea and bronchi were filled with a greenish exudate. Microscopic examination of the lungs showed focal areas of atelectasis. Many alveoli were filled with proteinaceous material. The tracheobronchial lymph nodes were enlarged.

DISCUSSION

A review of the family history in each of the five infants studied provides further information to support the genetic determination of glycogen storage disease of the heart. Two of our five patients were born to the same parents; a third male offspring in this family also died in early infancy and, although a post-mortem examination was not performed, showed an abnormal electrocardiogram compatible with the presence of glycogen storage disease of the heart. Thus, in a single family, there were probably three cases of glycogen storage disease, two females and one male, in addition to four older siblings who are living and well. Since the diagnosis in one male and one female infant was confirmed at autopsy, the conventional form of sex-linkage in the genetic transmission of this disease seems unlikely. In another instance, both an older half sibling of the same mother, and a younger subsequent sibling of the same parents are known to be free of glycogen storage disease of the heart. A review of the family history in this case revealed two neonatal deaths among siblings of the father. No definite history of consanguinity could be elicited in any of the families.

The obstetrical history in each of our five cases was not unusual. The birth weight of each of the five infants was above 3,000 grams except in the case of one premature infant who was one of twins, the sibling dying at the time of birth. The birth order of the involved infant within each family varied from the first to the eighth position. Three of the infants were males and two were females; four were Negroes and one white. Maternal age ranged from 25 to 30 years; paternal age from 28 to 50 years.

The average age of the patients on admission to the hospital was 4 months with a range of 2 to 7 months. Symptoms were first recognized at least one month prior to admission in four of the five cases and in two instances dated from the neonatal period. From the sequence of clinical events in these five patients, the onset of definite symptoms may be expected by the age of 4 to 6 months. The absence of symptoms at the age of 6 months would be strong evidence of the absence of this disease. The average age at the time of death was 6 months with a range of 4½ to 8½ months. No single factor seemed to be related to longer survival.

The hospital course in each instance was progressively downhill with occasional temporary plateaus associated with the successful treatment of secondary bacterial infections. Death in all instances resulted from aspiration, pulmonary infection, and pulmonary complications. In no instance was frank congestive heart failure observed. Because of the presence of respiratory distress and known cardiomegaly, digitalis was employed in two cases without apparent benefit. In both instances, digitalis intoxication was induced, suggesting the possibility that the myocardium in these infants was particularly sensitive to the effects of digitalis. The amount of digitalis administered prior to the appearance of toxic symptoms was relatively small in both instances.

The most striking physical findings noted in these five patients were those pertaining to the neuromuscular system. Paucity of spontaneous movements, generalized muscle weakness, and diminished deep tendon reflex responses were consistently present and progressive in all patients. Despite the obvious muscle weakness, palpation of the involved skeletal muscles in several instances revealed them to be of average or slightly greater than average size with a firm, rubbery consistency suggestive of muscles observed in pseudohypertrophic muscular dystrophy. Respiratory distress was also readily apparent as the result of the accumulation of secretions in the respiratory tract.

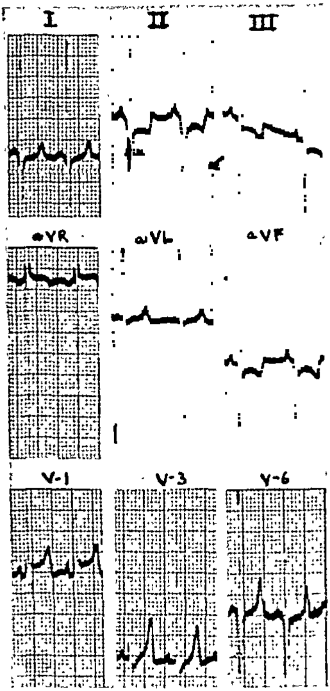
Attention was usually directed to the heart by the demonstration of cardiac enlargement either on physical examination or in routine roentgen examination of the chest. A cardiac murmur was detected in four of the five patients. These murmurs were of low intensity and low pitch, best heard to the left of the lower sternum or over the mid-precordium and would not ordinarily be considered significant murmurs. There were no associated thrills or diastolic murmurs. In only one of the five infants was a murmur audible over the posterior chest wall. Gross enlargement of the liver was never observed although the liver edge was palpable below the level of the right costal margin in four of five cases. The spleen was not palpable in any of our patients.

Approximately a dozen electrocardiographic tracings recorded from patients with glycogen storage disease of the heart have been reported in the medical literature to date; only about half of these have been reproduced and are available for review. In 1954, Johnson[13] outlined the electrocardiographic alterations observed in this condition in five tracings then available. He noted certain similarities among these tracings and listed the following characteristic features: (1) tall, upright QRS complexes in Leads I and II, inverted in Lead III; (2) depressed S-T segments in all standard leads; (3) inverted T waves in all standard leads; (4) elevated S-T segments in the right-sided precordial leads and depressed S-T segments in the left-sided precordial leads; (5) upright T waves in the right-sided precordial leads and inverted T waves in the left-sided precordial leads. Rossi[5] recently reported his observations on five additional tracings recorded from seven of his own patients with glycogen storage disease of the heart. A sinus tachycardia was present in all; high as well as low voltage complexes were observed, and right-sided as well as left-sided tracings were found to be compatible with this diagnosis. The consistent depression of S-T segments and the finding of negative T waves in the standard leads as well as in the left-sided precordial leads were also observed by Rossi.

Electrocardiographic tracings were available in four of the five infants described in this report, including precordial leads in three cases. A typical tracing is shown in Fig. 1. In general, the findings were similar to those previously reported. All tracings showed a sinus tachycardia or normal sinus rhythm. The QRS complexes were of very high amplitude in all of the four tracings; the average height of the R wave in standard Lead I was 28 mm. The P-R interval in the four tracings varied from 0.08 to 0.10 second; none were prolonged to the upper limit of normal. The Q-T interval varied from 0.27 to 0.29 second, also within the range of normal.

In Lead I the P waves were found to be notched in two tracings and to be peaked in Lead II in all four. The amplitude of P_2 was greater than 2.5 mm. in only one patient. The QRS complexes in the standard leads showed no axis deviation in any of the cases. The Q waves were of progressively increasing depth from Lead

I to Lead III. There was a prominent R wave over the right side of the chest in the three instances in which precordial leads were available. Over the left side of the chest the QRS complexes were diphasic with the R wave somewhat larger than the S wave. In Lead aV$_R$, a prominent S wave was present in two cases and a diphasic QRS was present in one instance.



recorded from three and one- storage disease muscle system Tracing demonstrates high amplitude QRS complexes, marked S-T and T-wave changes, and prominent Q waves in the limb leads; evidence of biventricular enlargement in the precordial leads

Depressed S-T segments were found in the limb leads in three of our four cases. This depression was of a severe degree, involving Leads II and III most commonly; Lead I also showed this abnormality in two cases. Negative T waves were present in all three standard limb leads in three of the four cases; in the remaining case, only in Leads II and III. Late inversion of T and negative T waves over the left chest were demonstrable in only one of the tracings.

These electrocardiographic abnormalities simulate those found among other primary myocardial diseases of infancy. On the basis of T-wave changes alone, glycogen storage disease cannot be differentiated with certainty from such lesions as primary endocardial fibroelastosis, aberrant origin of the left coronary artery arising from the pulmonary artery, interstitial myocarditis, and medial necrosis of the coronary arteries. However, study of the QRS complexes offers some information which is useful in attempting to differentiate the various entities in this group. For instance, in most cases of primary endocardial fibroelastosis and in all instances of aberrant origin of the left coronary artery arising from the pulmonary artery, the electrocardiogram should provide evidence of isolated left ventricular hypertrophy. A deep Q wave in Lead I and reciprocal changes in the S-T segments in Leads I and III may be present in the latter anomaly and should provide a means for differentiating these two conditions from each other. Glycogen storage disease of the heart and interstitial myocarditis are conditions in which the myocardium is diffusely and uniformly involved. Hence evidence of isolated left ventricular hypertrophy would not be anticipated in these two entities; evidence of biventricular cardiac enlargement is to be expected. The presence of generalized muscle weakness in glycogen storage disease should permit its differentiation from interstitial myocarditis.

Landing, Villee, and Nadas[14] made serial electrocardiographic observations in a patient with glycogen storage disease of the heart beginning at birth. A normal tracing was obtained at birth; this became abnormal between the tenth and twentieth day. The infant died at the age of one month and demonstrated the typical pathologic findings of glycogen storage disease of the heart. In this same infant the heart size on roentgen study was also within normal limits at the time of birth but was found to be enlarged on the twentieth day.

At least two roentgenograms were available for review in each of the five infants included in this report; the earliest film taken at the age of two months and the latest at seven months. The cardiac silhouette was strikingly similar among the five patients. In all instances, the cardiac shadow was moderately enlarged with a rounded or globular contour in all views, particularly the anteroposterior and left anterior oblique (Fig. 2 and 3). The cardiac enlargement in each case was of a diffuse nature with no specific chamber enlargement demonstrable. This feature may provide assistance in the differentiation of this condition from some of the other primary myocardial diseases of infancy, especially from those conditions in which left ventricular enlargement

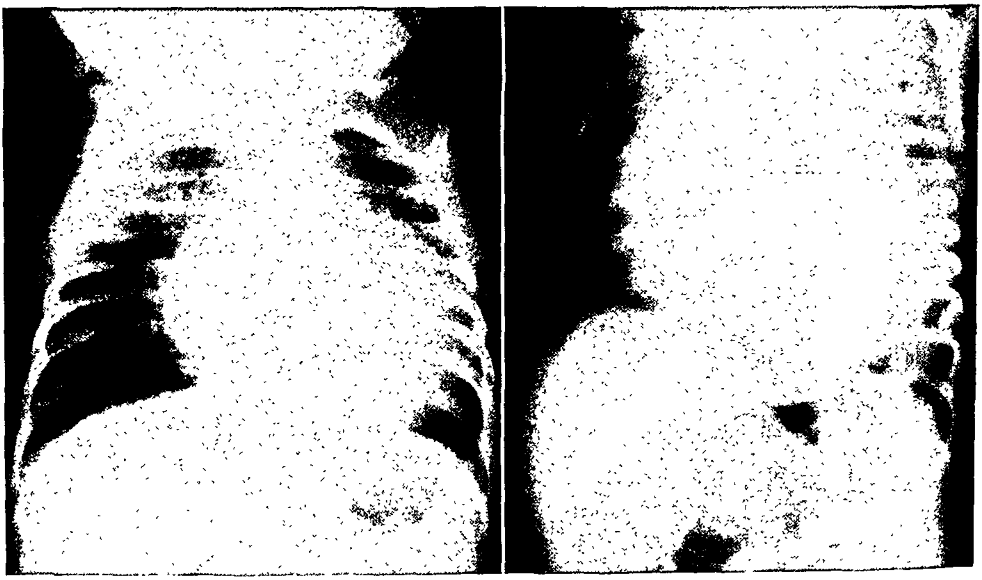


Fig. 2.—Roentgenograms of the chest taken in the anteroposterior and left anterior oblique views at the same time and from the same patient, as the electrocardiogram shown in Fig. 1, showing a moderate degree of cardiac enlargement with a globular cardiac contour.

usually predominates, e.g., aberrant origin of the left coronary artery from the pulmonary artery and endocardial fibroelastosis. Among the five patients presented here, a moderate degree of cardiac enlargement was the rule; none showed massive and only one showed slight cardiac enlargement. The heart showed little change in size during the period of observation which ranged up to two months. Neither the pulmonary artery segment nor the peripheral vascular markings were especially prominent, although the problem of differentiating pulmonary infection from congestive heart failure arose in one case. In four of the five patients, pulmonary infection and/or atelectasis were present, usually involving the left lower lobe. Aspiration was thought to play a major role in the development of these pulmonary complications although cardiac enlargement with bronchial compression may also have been a factor. No pleural fluid was observed.

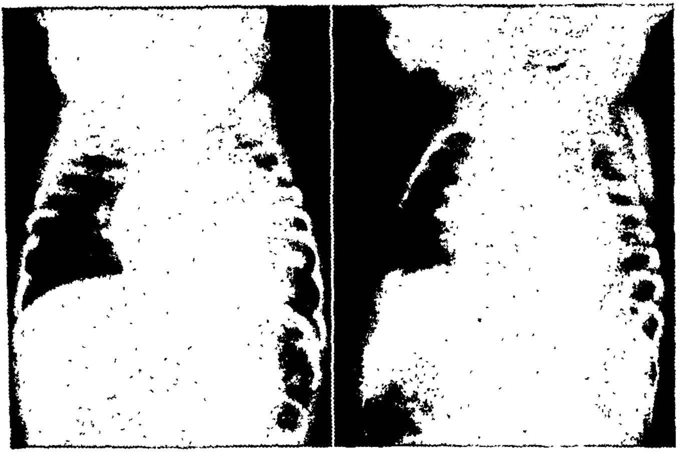


Fig. 3.—Roentgenograms of the chest in the anteroposterior and left anterior oblique views from a 5-month-old infant who died two months later from glycogen storage disease of the heart and skeletal muscles. Note similarity of *general cardiac contour* on comparison with Fig. 2. Also, in the anteroposterior view, the triangular-shaped double density appearing within the cardiac shadow is probably atelectasis of the left lower lobe.

The diagnosis most commonly made at the time of admission or at the time of discovery of definite muscle weakness was amyotonia congenita or Werdnig-Hoffmann's disease. In no instance was the initial impression that of heart disease. In two instances the sluggish appearance of the baby with a large projecting tongue and flabby musculature suggested cretinism and/or mongolism. Two of the infants were given Prostigmin in order to rule out the diagnosis of myasthenia gravis; they showed no response. In some instances the cardiac involvement only became evident when a roentgenogram and/or electrocardiogram was recorded. The diagnostic problem was best resolved by carrying out a skeletal muscle biopsy. In each of our four cases examined in this way the muscle fibers showed vacuoles containing material with the staining characteristics of glycogen. Generalized muscle weakness was clinically evident at this time in all four instances. The absence of abnormal liver function tests, a normal response to epinephrine, and no response to Prostigmin were also useful indirect or negative contributions to the diagnosis.

In the course of the diagnostic investigation of the five infants included in this report, a host of laboratory tests were carried out. The results of these tests were similar to those found in the case described above and in those previously reported in patients with this disease; a mild normochromic anemia, normal routine urinalyses free of excessive sugar and acetone, normal response of blood sugar levels to epinephrine administration, normal liver function tests and blood chemistry studies. In addition, a few less commonly performed studies were carried out which are worthy of mention even though negative results were also obtained. Electromyographic recordings from the flexor digitorum sublimus of one infant showed normal motor unit potentials of decreased amplitude and decreased frequency consistent with a myopathy. There was no evidence of abnormal electrical activity such as might be associated with an intrinsic neurological condition. Chronaxie determinations from arm and leg muscles were normal, indicating no evidence of denervation. Ellis[15] earlier reported a normal response to faradic current stimulation. The serum glycogen level was determined in one case to be 8.16 mg. per cent; normal subjects tested simultaneously demonstrated serum glycogen levels of 20 to 25 mg. per cent. In one patient an electroencephalogram was reported to show no evidence of cerebral dysrhythmia. A normal ventricular system was also demonstrated in this patient on pneumoencephalography.

Specimens of skeletal and cardiac muscle from two patients were studied in the laboratory of Dr. Gerty T. Cori. The findings in one case are included in the case above. In the other instance the glycogen structure was also reported to be normal; an average 37 per cent of the glucose residues of each glycogen molecule were in the outer branches, which is within the range of "normally occurring" glycogens. No enzyme deficiency was found.

The pathologic changes, both gross and microscopic, found in this disease have been adequately described.[16] In the five specimens available for review, obvious cardiac enlargement was present in all instances, the average cardiac weight being 108 grams as compared to 36 grams for comparable normal infants.[17] In all instances the average left ventricular wall thickness was three times greater in these specimens than the average right ventricular wall thickness. The relationship of the left and right ventricular wall thicknesses was approximately the same as is seen normally at a comparable age, suggesting that all portions of the heart muscle are evenly and diffusely involved. No additional gross congenital cardiac anomalies were noted in any of the specimens.

The microscopic examination of the myocardium showed fibers of increased size with prominent, irregular, hyperchromic nuclei. The sarcoplasm was displaced to the periphery of the cells by a wide clear zone of material which had the staining characteristics of glycogen.

The finding of glycogen deposition on microscopic examination of the myocardium is not uncommon and is per se not specific for any one disease process. Mowry and Bangle[18] found glycogen in the myocardium of six of thirty-three infants dying of variable causes unrelated to any type of glycogen storage disease. The presence of glycogen in the myocardium of diabetic patients is also well recognized.[19] Thus, the finding of diffusely deposited glycogen in the myocardium is not in itself specific for either the hepatic or cardiac type of glycogen storage disease. In general, a quantitatively greater degree of infiltration will be found in the heart in the cardiac form as compared to the hepatic form of glycogen storage disease, although considerable deposition occurs in all organs of the body in both forms. Localized accumulations of glycogen in the myocardium are also known to occur and have been variously referred to as solitary and multiple cardiac rhabdomyomatosis, congenital glycogenic tumors of the heart, congenital nodular glycogenic degeneration of the myocardium, and by other titles.[20, 21, 22] These lesions are apparently not diseases of deposition of glycogen but are considered to be either tumors or developmental malformations associated with some degenerative process. A variety of other congenital cardiac anomalies in which myocardial hypertrophy and perhaps myocardial ischemia are present may also be associated with the deposition of glycogen in the myocardium. In infants born of diabetic mothers and in infants dying of erythroblastosis fetalis,[5] glycogen storage in the myocardium has also been observed. Thus, the pathologic diagnosis of glycogen storage disease of the heart cannot be made on the basis of glycogen deposition in the myocardium alone.

SUMMARY

1. The clinical findings in five infants with glycogen storage disease of the heart and skeletal muscle system have been summarized. Emphasis has been placed upon the prominent role played by generalized muscle weakness and its complications rather than the cardiac manifestations in this entity.

2. The electrocardiographic findings in four patients with this disease are presented in detail because of the relative paucity of previously reported tracings.

3. Some problems pertaining to the differential diagnosis, both clinical and pathologic, of glycogen storage disease of the heart and skeletal muscle system have been discussed.

We are indebted to Dr. Gerty T. Cori of St. Louis, Missouri, for the chemical analysis of tissue specimens carried out in two cases.

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FURTHER STUDIES ON THE CARDIOVASCULAR STATUS OF NORMAL NEWBORN INFANTS

IV. Effect of Adrenaline, Acetylcholine, 10 Per Cent Oxygen, and 100 Per Cent Oxygen on the Electrocardiogram

Claude Dupuis, M.D.,[*] Bracq Dupuis, M.D.,[*] Forrest H. Adams, M.D.,[**]
John Lind, M.D., and Tuomas Peltonen, M.D.

INFORMATION accumulated recently[1-6] indicates that the cardiovascular system of the normal newborn infant adjusts gradually over a period of several days rather than within minutes after birth as previously supposed.[7] The change from the fetal type of circulation to the newborn circulation is probably brought about by the following factors: an increase in systemic resistance; a decrease in pulmonary resistance; an increase in the arterial oxygen saturation; and other less well-defined factors.[8] Associated with these fundamental changes in the cardiovascular system is the presence of a large left-to-right shunt through the ductus arteriosus at rest[2, 5, 6] and a right-to-left shunt with crying[1, 4] and right ventricular and pulmonary artery hypertension.[5, 6] During this period of adjustment, the newborn infant's cardiovascular system responds to adrenaline and noradrenaline with an increase in right ventricular and pulmonary artery pressure; and adrenaline produces a tachycardia whereas noradrenaline produces a bradycardia.[9] Acetylcholine, 100 per cent oxygen, and 10 per cent oxygen with 90 per cent nitrogen appear to produce no significant effect on the right ventricular pressure of such infants.[9] These responses and findings in the normal newborn infant have been found to be somewhat different from those obtained in newborn animals.[10, 11]

The complexity of direct measurement of right heart pressures, shunts, and resistance suggests the need for simpler methods of measuring these changes. For these reasons, it seemed of interest to evaluate the role of the electrocardiogram in such studies. Ziegler[12] has recently reported the electrocardiographic changes during the first few hours and days of life as part of an over-all survey of the electrocardiographic findings in normal infants and children. In this connection, James[13] has suggested that the T wave in unipolar Lead V_1 may reflect in part the pressure in the right ventricle and pulmonary artery.

This paper presents the results of an investigation on the effects of adrenaline, acetylcholine, 100 per cent oxygen,

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and 10 per cent oxygen on the electrocardiogram in normal newborn infants ranging in age from birth to 9 days. Cardiac catheterization was not performed as a part of these investigations.

MATERIALS AND METHODS

All of the newborn infants studied in this report were selected after history and physical examination had demonstrated that each was free from cardiovascular disease. No heart murmurs were recorded on the phonocardiogram.

Group I consisted of 30 infants born in the University Hospital at Turku, Finland. Electrocardiograms were recorded daily for the first 3 to 4 days of life by use of the conventional techniques and leads recommended by Ziegler.[12]

Groups II and III were comprised of 25 infants each born in the Södrabarnbordhuset, Stockholm, Sweden. The 25 infants of Group II were under 24 hours of age and the 25 of Group III were between 5 and 9 days of age. This later age period was selected to compare with the former since it is thought that the major neonatal circulatory adjustments are completed by 5 days of age under normal circumstances.[5, 6] In these two groups of infants, the three standard biopolar, the three unipolar extremity, and unipolar Leads V_1 and V_5 were recorded in each.

Group IV consisted of 10 infants under 24 hours of age. In each infant, a base-line electrocardiogram was obtained, as mentioned, for Groups II and III. With the electrocardiogram recording unipolar Lead V_1, five of the infants (Group IVa) were given 50 μg of acetylcholine (2 intravenously and 3 intramuscularly) and a continuous recording was made for five minutes. In five other infants in this age period (Group IVb) 100 per cent oxygen was administered by a small hood for periods of 10 to 20 minutes during which time electrocardiographic tracings were periodically made of unipolar Lead V_1.

Group V consisted of 12 infants 5 to 10 days of age. As in Group IV, base-line electrocardiographic tracings were obtained in each. With the electrocardiogram recording unipolar Lead V_1, six of the infants (Group Va) were given 50 μg of adrenaline intramuscularly and a continuous recording was made for five minutes. In two infants, 97 and 98, a second dose of 100 μg of adrenaline was given. and followed similarly; two others 95 and 96 received only 100 μg of adrenaline. In four other infants (Group Vb) 10 per cent oxygen with 90 per cent nitrogen was administered by a small hood for 10 minutes during which time electrocardiographic tracings were periodically made of unipolar Lead V_1.

All of the electrocardiograms were taken with a direct writing apparatus of the "jet" type (Elema Mingograph) using small electrodes. The concentration of the gas mixtures entering the baby was checked in each case with a Beckman oxygen analyzer, the sampling tip of which was placed at the nostrils. Readings were made periodically during each study. Measurements of the electrocardiographic tracings were made according to the recommendations of Ziegler.[12]

RESULTS

Table I summarizes the pertinent results obtained in the *longitudinal* studies of the thirty infants in Group I ranging in age from birth to 4 days. Each infant with the age at the time of study is listed. There were 16 female infants and 14 male infants. All had normal weights and lengths. In 19 of the 33 infants, the electrocardiographic axis deviation decreased with time, but these variations were frequently slight and of little significance. All showed evidence of right ventricular hypertrophy as manifest by prominent RV_1 and SV_5. The T wave in V_1 was positive in all infants prior to 12 hours of age and positive in most up to 24 hours of age. After this time, TV_1 frequently became diphasic and then negative. There appeared to be no relationship between TV_1 and the axis deviation or RV_1 and SV_5. TV_5 was usually positive, but it was negative on six occasions, including 3 times in infant No. 20. The ventricular activation time of V_1 in all infants was 0.02 second or less.

Table II summarizes the pertinent results obtained in the *cross-sectional* studies of the 25 infants in Group II; all were under 24 hours of age. There were 13 male and 12 female infants; all had normal weights and lengths. They are arranged according to increasing age, the youngest was 1 hour and the oldest was 24 hours. The mean axis deviation was 130 degrees with a range of 105 to 170 degrees. As in Group I, all showed evidence of right ventricular hypertrophy as manifested by a prominent RV_1 and SV_5. The T wave in V_1 was positive in those infants under 12 hours of age. Between 12 and 24 hours of age there were 4 infants who had diphasic and 3 who had negative T waves in V_1.

Table III summarizes the pertinent results obtained in the *cross-sectional* studies of the 25 infants in Group III, all of whom were between 5 and 9 days of age. There were 16 male and 9 female infants; all had normal weights and lengths. They are arranged according to increasing age; the youngest was 5 days and the oldest was 9 days. The mean axis was 130 degrees with a range of 103 to 185 degrees. As in Groups I and II, all infants showed evidence of right ventricular hypertrophy. The T wave in V_1 was negative in 20 infants and slightly diphasic in 5 infants. The major diphasic component in this later group was always negative.

The results of the administration of 50 μg of acetylcholine to five infants are summarized in Table IV. These infants ranged in age from 5 hours to 30 hours. In two, the drug was given intravenously and in three it was given intramuscularly in the arm. Although some inconsistent changes in the heart rate occurred, no other effects were observed on the electrocardiogram including the amplitude of the T wave in V_1 which was positive in each case.

The results of breathing 100 per cent oxygen obtained in five infants for ten to twenty minutes are summarized in Table V. These infants were between 1 hour and 25 hours of age. The heart rate frequently decreased slightly but not invariably. The T wave in V_1 was positive in all prior to, during, and following the procedure. The oxygen appeared to have no effect on it or any other part of the electrocardiogram. All of the babies appeared agitated and 3 infants vomited.

Group V contained those infants 5 to 10 days of age. In six of these, 50 μg of adrenaline was given intramuscularly, two of whom received a second

TABLE I. LONGITUDINAL ELECTROCARDIOGRAPHIC FINDINGS IN 30 NORMAL NEWBORN INFANTS FROM BIRTH TO 4 DAYS OF AGE (GROUP I)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
1	F	3,000	50	3	140	108	15	10	2	4	19	−1 +1
				27	128	106	9	4	−2	6	18	1
				56	112	108	12	11	−2	3	10	2
2	F	3,000	50	1	132	139	6	10	2	10	8	2
				25	130	142	8	9	2	8	12	2
				25	128	160	8	4	−1	7	12	2
3	M	3,250	50	13	135	142	10	2	7	10	11	1
				25	148	142	13	7	−2 +1	3	7	1.5
				49	118	132	10	7	−3	15	12	0.5
4	F	3,900	50	12	125	110	10	3	2	12	6	1
				36	120	100	8	3	−2	15	7	1
				60	110	122	5	0	−2	10	12	3
5	M	3,500	52	8	130	118	11	8	1	6	7	1
				31	150	144	11	9	2	8	20	2
				55	162	122	13	4	−1 +1	11	17	1
6	F	3,470	50	12	130	122	10	8	−2	12	9	1
				36	115	148	12	9	−2	14	7	1
				60	108	136	7	3	−2	8	3	2
7	F	4,250	52	22	130	135	10	10	−1 +1	4	11	1
				46	124	130	10	8	−2	3	8	0.5
				70	122	125	11	16	−2	5	12	2
8	M	3,580	51	25	152	142	14	0	−1 +1	11	30	3
				49	145	140	12	0	−3	8	15	2
				36	128	130	6	0	−1	16	24	2
9	M	3,600	51	10	114	110	5	11	1	4	5	0.5
				34	110	120	10	15	−2 +1	5	9	2
				58	112	108	5	11	−1 +1	7	8	2
10	F	4,300	54	23	152	118	8	3	−2	5	15	1
				47	180	118	12	8	−2	3	12	2
				71	128	142	7	3	−2	5	12	2

11	F	3,200	51	18	152	130	9	3	1	10	12	2
				42	158	135	12	4	−1 +1	5	15	1
				65	145	124	15	3	−1 +1	12	15	2
12	F	4,300	54	20	125	138	10	8	3	5	10	1
				44	124	148	12	2	−1 +1	7	14	1
13	F	3,100	51	68	135	132	8	2	−2	10	18	1
				17	118	112	20	2	1	13	8	2
				39	115	108	8	1	−1 +1	14	12	2
14	M	3,780	52	63	104	118	20	2	−2	15	7	1
				25	172	148	9	4	2	8	13	2
				49	155	150	22	13	−2 +2	9	20	2
				74	150	130	17	9	−3 +1	7	20	2
15	M	3,500	51	26	175	112	14	2	2	5	15	1
				50	170	150	12	8	−3	5	12	2
				75	158	124	14	2	−3	5	18	2
16	F	3,100	50	27	102	140	9	4	1	17	30	2
				56	118	130	10	2	1	12	22	−2
				80	118	148	18	5	−3 +1	14	18	2
17	M	4,080	51	35	150	140	8	0	−1 +1	8	15	2
18	F	3,450	51	58	160	135	8	2	−2	7	12	1
				82	152	134	10	1	−2	5	12	2
				8	132	118	15	1	2	14	15	1
				32	128	132	18	11	−2 +2	8	14	1
19	F	2,420	45	57	120	132	20	2	−2	12	16	1
				25	120	110	8	5	−2	14	5	1
				49	112	148	10	12	−4	10	14	2
				72	106	140	10	8	−5	5	8	2
20	F	3,620	31	26	112	148	8	0.5	1	21	13	−3
				50	105	135	9	4	1	21	12	−2
				73	102	148	10	4	1	28	13	−2

TABLE I—CONT'D

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
21	M	3,240	51	27	118	142	12	8	1	5	15	2
				50	120	154	15	8	−1	12	30	2
				74	120	152	13	2	+1 −4	12	17	3
22	F	4,320	52	37	122	148	8	5	−1	9	24	1
				60	134	128	15	9	−2	8	13	1
				84	134	165	15	5	−2	10	15	0.5
23	M	4,150	54	34	170	122	7	4	−2	2	9	1
				68	180	140	12	9	+1 −3	5	9	1
				92	158	130	14	7	−2	6	15	2
24	M	3,540	53	46	165	135	23	4	−2	6	19	2
				70	170	132	30	8	+1 −3	3	9	2
				94	165	138	20	5	−5	5	11	2
25	M	2,450	45	22	125	136	12	5	−2	10	12	1
				46	118	156	12	6	−2	11	14	1
				72	110	152	7	1	−1	9	7	2
26	F	4,530	55	6	155	145	9	5	3	2	10	−2
				53	138	142	10	1	−2	4	15	3
				77	152	140	15	3	−3	2	18	2
27	F	3,770	51	6	122	132	11	1	2	10	13	1
				30	124	138	11	0	2	7	4	1
				75	130	124	9	2	−2	4	3	2
28	M	4,000	52	13	120	122	7	5	+1 2	5	3	1
				38	170	120	15	5	−4	10	11	2
				85	180	152	15	3	−3	5	10	2
29	M	3,230	49	26	152	145	19	10	−3	10	15	2
				44	155	152	20	6	+2 −3	14	9	2
				118	132	148	10	4	+1 −3	20	11	−2
30	M	3,440	50	44	152	150	12	0	−2	3	11	1
				91	165	136	13	1	−1	11	13	3
				103	168	124	10	0	−2	5	10	3

TABLE II. CROSS SECTIONAL ELECTROCARDIOGRAPHIC FINDINGS IN 25 NORMAL NEWBORN INFANTS UNDER 24 HOURS OF AGE (GROUP II)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (HOURS)	AXIS DEVIATION (DEGREES)	HEART RATE PER MIN.	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
31	M	3,500	50	1	120	130	18	5	3	6	15	1
32	M	3,130	50	2	140	120	12	0	2	1	17	1
33	M	3,710	49	3	138	115	9	5	1	15	15	2
34	F	3,000	50	4	120	150	7	1	5	15	19	4
35	M	3,800	51	5	155	122	12	0	1	6	5	1
36	F	3,220	50	5	150	132	10	9	2	22	15	3
37	F	3,770	51	10	118	132	15	0	4	12	5	1
38	F	2,945	49	11	150	130	10	11	2	2	4	0.5
39	M	3,380	50	11	115	108	12	25	4	7	8	1
40	F	3,500	50	12	105	150	15	13	5	8	5	−1
41	M	3,520	50	12	144	120	13	2	−2 +1	8	8	1
42	M	3,420	50	14	122	114	15	13	3	11	23	1
43	M	3,430	50	15	120	110	15	10	2	8	9	1
44	F	3,300	48	15	124	120	10	4	2	11	9	1
45	F	2,730	50	15	120	132	9	20	−1 +1	10	18	1
46	F	2,500	49	15	115	145	15	5	−1	10	10	−2
47	M	3,080	47	15	120	122	13	12	3	10	12	2
48	F	3,500	51	18	122	130	13	7	−2	15	11	+1
49	F	3,150	51	19	112	136	10	10	−4	8	7	2
50	M	3,400	51	20	152	138	9	3	2	7	18	1
51	M	3,800	51	22	130	135	9	8	1	4	19	2
52	F	3,500	50	22	110	115	16	22	−2 +2	16	16	1
53	M	3,240	50	23	170	130	13	4	2	17	25	2
54	M	3,300	50	23	120	105	12	4	1	10	5	1
55	F	3,570	51	24	125	145	16	9	−1 +1	15	15	−2

TABLE III. CROSS-SECTIONAL ELECTROCARDIOGRAPHIC FINDINGS IN 25 NORMAL NEWBORN INFANTS BETWEEN 5 AND 9 DAYS OF AGE (GROUP III)

INFANT	SEX	WEIGHT (GRAMS)	LENGTH (CM.)	AGE (DAYS)	AXIS (DEGREES)	HEART RATE	RV_1 (MM.)	SV_1 (MM.)	TV_1 (MM.)	RV_5 (MM.)	SV_5 (MM.)	TV_5 (MM.)
56	M	3,590	50	5	152	120	16	8	–3 +2	10	5	1
57	F	3,000	50	5	110	108	7	4	–3	15	12	2
58	M	3,980	51	5	154	110	16	5	–2	15	10	2
59	M	3,600	51	5	132	130	20	7	–5	5	15	3
60	F	2,760	49	5	103	140	15	12	–6	12	9	2
61	M	4,300	52	5	148	142	12	14	–2	6	12	3
62	F	3,270	50	5	160	132	14	5	–5	11	15	1
63	F	3,000	50	5	125	135	9	7	–5	11	10	0
64	M	2,850	48	5	170	128	11	4	–3	13	15	3
65	F	2,760	50	5	130	135	16	8	–4	20	8	–2
66	M	3,430	50	5	110	134	20	7	–6	12	12	–1
67	M	3,980	52	6	128	125	15	3	–2	13	14	–2
68	M	3,250	50	6	145	132	6	5	–2	4	16	1
69	M	4,250	51	6	126	118	13	10	–2 +1	14	12	2
70	M	3,720	51	6	180	152	23	15	–6 +3	12	18	3
71	F	3,700	51	6	125	144	13	10	–5	6	9	1
72	M	4,210	52	6	175	134	12	3	–2	5	14	3
73	M	4,570	52	6	144	128	13	5	–4	13	16	1
74	F	3,620	50	6	110	135	14	17	–3 +1	15	8	2
75	M	3,800	51	6	155	150	9	6	–4	8	16	3
76	M	4,280	51	7	128	145	20	17	–5	17	13	2
77	F	2,500	49	8	122	170	10	9	–5	17	10	2
78	F	3,200	51	8	158	144	9	1	–3	13	15	2
79	M	3,300	50	8	185	148	9	4	–5	7	18	1
80	M	3,000	49	9	110	106	8	10	–2 +1	10	10	3

TABLE IV. EFFECT OF 50 μG ACETYLCHOLINE IN 5 NORMAL INFANTS
(Group IVa)

INFANT	81			82			83			84			85		
AGE (HOURS)	5			15			5			30			16		
ROUTE	I.M.			I.M.			I.M.			I.V.			I.V.		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	135	–	2	105	–	2	120	–	2	135	–	3	110	–	3
15	135	0	2	105	0	2	128	7	2	135	0	3	110	0	3
30	105	–23	2	105	0	2	120	0	2	140	4	3	110	0	3
45	135	0	2	105	0	2	–	–	–	135	0	3	110	0	3
60	135	0	2	140	33	2	115	–4	2	135	0	3	105	–4	3
120	105	–23	2	135	28	2	115	–4	2	130	–4	3	105	–4	3
180	130	–4	2	115	9	2	120	0	2	135	0	3	105	–4	3
300	145	8	2	105	0	2	128	7	2	130	–4	3	105	–4	3

TABLE V. EFFECT OF 100 PER CENT OXYGEN ADMINISTERED BY HOOD TO 5 NORMAL INFANTS
(Group IVb)

INFANT	86			87			88			89			90		
AGE (HOURS)	11			23			1			20			25		
TIME (MINUTES)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	110	–	4	125	–	4	125	—	2	140	—	2	100	—	4
2	105	–4	4	120	4	4	120	–4	2	135	–3	2	80	–20	4
4	100	–9	4	120	–4	4	125	0	2	120	–14	2	90	–10	4
6	100	–9	4	135	8	4	125	0	2	130	–7	2	85	–15	4
8	75	–32	4	125	0	4	120	–4	2	130	–7	2	95	–5	4
10	110	0	4	135	8	4	115	–8	2	120	–14	2	85	–15	4
12	96	–	–	115	–8	4	125	0	2	125	–10	2	80	–20	4
14	90	–18	4	125	0	4	125	–4	2	120	–14	2	106	6	4
16	100	–9	4	125	0	4	120	–4	2	135	–3	2	82	–18	4
18	110	0	4	130	4	4	120	–4	2	135	–3	2	84	–16	4
20	120	9	4	130	4	4	—	—	–	—	—	–	132	32	4

(Group Va)

INFANT AGE (DAYS) DOSE	91 5 50 µg			92 5 50 µg			93 6 50 µg			94 5 50 µg			95 5 100 µg		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)
0	135	—	−4	125	—	−5	120	—	−3	110	—	−3	176	—	−5
15	150	11	−4	175	40	d{−4, +4}	135	13	d{−3, +2}	165	50	−3	176	0	d{−5, +5}
30	140	4	d{−5, +2}	175	40	d{−4, +7}	120	0	d{−4, +2}	165	50	−4	170	−3	d{−3, +3}
45	150	11	d{−4, +1}	180	44	d{−4, +7}	105	−13	d{−2, +1}	165	50	−7	165	−6	d{−3, +3}
60	150	18	−5	180	44	−6	105	−13	d{−3, +1}	105	−1	d{−2, +3} ← E.	100	−42	{ 5
120	150	11	−5 N.E.	180	44	−5	90	−25	d{−3, +1}	100	−8	d{−3, +2}	88	N.R. → −50	d{−4, +3}
180	140	4	−4	120	−4	−5	110	−9	−3	110	0	−5 } Big.	95	−45	d{−5, +2} }
300	135	0	−4	150	20	d{−6, +7}	120	0	−3	90	−17	−8 }	110	−32	−5

INFANT AGE (DAYS) DOSE	96 6 100 µg			97 9 50 µg			97 9 100 µg			98 10 50 µg			98 10 100 µg		
TIME (SECONDS)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)	HEART RATE	RATE % CHANGE	TV₁ (MM.)
0	150	—	−5	105	—	d{−3, +1}	140	—	−3	170	—	−3	170	—	−3
15	—	—	—	165	52	d{−5, +1}	160	14	−5	180	6	−3	150	−12	−3
30	—	—	—	150	43	d{−6, +1}	180	28	−5	180	6	−4	190	12	−3
45	—	—	—	145	40	d{−5, +2}	160	14	d{−4, +1}	165	−3	−6	170	0	−3
60	160	7	d{−7, +1}	150	43	d{−8, +1}	155	10	d{−4, +1}	185	8	−8	150	−12	{ d{−3, +2}
120	155	3	d{−2, +2}	135	28	d{−7, +1}	110	−22	d{−3, +1}	150	−12	d{−3, +2} ← N.E.	140	N.E. → −18	d{−3, +2}
180	155	3	d{−3, +2}	135	28	d{−7, +1}	100	−29	d{−4, +1}	180	6	−6	120	−30	−3 }
300	—	—	—	114	9	−6	140	0	−7	180	6	−3	135	−20	−4

Key: N.R. = nodal rhythm. E. = extrasystole. Big. = bigeminal rhythm. N.E. = nodal extrasystoles. d = diphasic.

injection of 100 µg. The results of these studies are summarized in Table VI. Commonly there was an increase in heart rate of variable degree; however, a few showed bradycardia due to disturbances of rhythm. There were 2 instances of nodal rhythm, 3 of nodal extrasystoles, and 1 of bigeminal rhythm. In all instances, changes occurred in TV_1, which prior to administration of adrenaline was negative. In one instance, it became positive and in the others it became diphasic. The infants responded by manifesting agitation and early suffusion followed by paleness and tachypnea.

Ten per cent oxygen in 90 per cent nitrogen was administered by hood for 10 minutes to four infants of Group Vb. The results are summarized in Table VII. Three were 6 days of age and one was 8 days old. All infants became cyanotic and somnolent. The heart rate increased somewhat, but not consistently. No changes were observed on the electrocardiogram including TV_1.

TABLE VII. EFFECT OF 10 PER CENT OXYGEN ADMINISTERED BY HOOD TO 4 NORMAL INFANTS (Group Vb)

INFANT AGE (DAYS)	99 6			100 6			101 6			102 8		
TIME (MINUTES)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)	HEART RATE	RATE % CHANGE	TV_1 (MM.)
0	150	—	–3	125	—	–3	105	—	–3	150	—	–3
2	160	7	–3	105	–16	–3	120	15	–3	150	0	–3
4	162	8	–3	100	–20	–3	118	13	–3	172	14	–3
6	162	7	–3	120	–4	–3	120	15	–3	153	2	–3
8	166	10	–3	140	12	–3	125	20	–3	150	0	–3
10	165	10	–3	105	–16	–3	122	17	–3	150	0	–3

DISCUSSION

The results of these studies on the electrocardiographic changes with age in the normal newborn infant are in general agreement with the earlier reported findings of Ziegler.[12] Specifically the T wave in unipolar Lead V_1 was regularly positive under 12 hours of age and negative or diphasic after 5 days of age. The transition between these two phases was gradual and took place over the same time interval that the pulmonary hypertension normally disappears.[5, 6] Evidence of right ventricular hypertrophy, however, persisted throughout this entire period without significant change. Administration of adrenaline to infants with presumably normal pulmonary artery pressures frequently produced changes in the T waves of the electrocardiogram similar to those found in infants *with* pulmonary hypertension.

Earlier attempts by us to reduce the pulmonary hypertension in infants under 24 hours of age by administration of acetylcholine or breathing 100 per cent oxygen were unsuccessful.[9] The negative results in these electrocardiographic studies are consistent with the earlier observations. This lack of effect of acetylcholine on the pulmonary hypertension of newborn infants is in constrast to its effect in adults[14-16] and animals[10, 11] with pulmonary hypertension. The negative effect of 100 per cent oxygen in these infants is also in constrast to its effect in some adults with pulmonary hypertension.[17]

The inability to alter significantly the electrocardiographic pattern of newborn infants by administration of either 10 per cent or 100 per cent oxygen speaks against acute anoxia or anoxemia as a common cause of the findings.[18]

In spite of the results of these studies and of those reported previously, it is still difficult to make any positive statements regarding the nature of the pulmonary hypertension in the normal newborn infant. Further studies are *indicated.*

SUMMARY

The electrocardiographic changes in the normal newborn infant during the first 10 days of life were investigated. Thirty infants were studied longitudinally and seventy-two were studied cross-sectionally. The physiologic response of certain of the latter group of infants to administration of 10 per cent and 100 per cent oxygen by mask and to adrenaline and acetylcholine was measured recording unipolar Lead V_1.

Changes with age reported earlier by Ziegler were confirmed. Alteration of the T wave in V_1 took place over the same time interval that the pulmonary hypertension normally disappears. In older infants, administration of adrenaline produced changes in the T wave of V_1 similar to those found in younger infants who normally have pulmonary hypertension.

Administration of 100 per cent oxygen to the younger infants and 10 per cent oxygen to the older infants produced no significant alteration in the electrocardiographic tracing of V_1, other than minor changes in the rate. Likewise, administration of acetylcholine to the younger infants produced no significant change in the pattern.

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Piece of Tin in the Windpipe. Laryngo-tracheotomy.—Dr. Paul F. Eve records (*Nashville Journ. Med. and Surg.*, Sept., 1857) the case of a negro boy, three years of age, which strongly illustrates the occasional great power of endurance of the human system. The patient two days before being taken to Dr. E., "while attempting to whistle with a small strip of tin in his mouth, fell backwards out of a piazza and inhaled it into his windpipe. This was followed by instant and persistent embarrassment to respiration, loud rhonchus, loss of voice, or rather its reduction to a whisper, and some slight hemorrhage. The family physician not having relieved the patient by an emetic, inversion of the body, etc.," directed the boy to be taken to Nashville. Being satisfied from the symptoms that there was a foreign body in the windpipe, Dr. E. decided to operate. Accordingly, on the 13th June, four days after the accident, Dr. E. opened the larynx, and then the trachea, and made "diligent search" for the foreign substance. The larynx was twice wiped out by sponges carried through the wound and brought out of the mouth, and the trachea and bronchi carefully and cautiously explored with probes and long forceps, but nothing special detected. There was an unusual amount of hemorrhage in the division of the soft parts, and ligatures were applied to each side of the isthmus of the thyroid body before its section. Dr. Bowling administered the anaesthetic agent (equal portions of ether and chloroform), while Drs. Jennings, Briggs, Wharton and others aided during the operation, which to any one who has never opened the windpipe of a fat child three years old, it would be unnecessary to say, was a tedious and embarrassing one.

The second morning, during a paroxysm of cough, a piece of tin, measuring seven-tenths of an inch in length, and three-twentieths in width, with sharp angles and edges, was ejected through the wound. It was smooth and polished upon its two surfaces, discolored, however, now by bloody mucus. Treatment, antiphlogistic, continued.

In a day or two the patient began to improve, and on the tenth day left for home.

TRUE HERMAPHRODITISM

Report of a Case

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THE first "hermaphrodite" was presented not in medical literature, but as an amazing creation in Greek mythology from the union of Hermes and Aphrodite. For hundreds of years this remarkable creature, with attributes of both male and female, was deified in romantic literature and the arts. It was not until the latter part of the nineteenth century that the subject was approached scientifically in medical literature.[1] Young's[2] classical monograph in 1937 presented 20 acceptable cases of true hermaphroditism that had appeared in the literature up to that time. A case reported by Gudernatsch[3] in 1911 was later accepted by Young. In 1944, McIver, Seabaugh and Mangels[4] reviewed 13 additional cases. Fischer, Lischer, and Byars,[5] in 1952, listed 14 subsequent cases and added one of their own. In 1956, Schwiebinger and Hodges[6] presented the fifty-fifth case of true hermaphroditism after mentioning 5 other acceptable cases. Considering 14 additional and recently reported cases,[7-19] the patient presented here apparently is the seventieth case of true hermaphroditism in the medical literature, and the eighteenth case of the lateral or alternating type.

Undoubtedly, this condition is much more frequent in occurrence than its appearance in medical archives would lead one to believe. We are aware of 3 cases of true hermaphroditism from other hospitals in Memphis that have not yet been published.[20, 21] Recently, Clayton, O'Heeron, and Smith[22] have published a case report. Most of the patients in the reported cases were not seen or diagnosed by a physician before adolescence and were thus subjected to the early psychologic trauma because of their anomaly. It is academic to point out that preventive therapeutics (medical, surgical, and psychologic) will produce more satisfying results when the correction of such a condition is accomplished before the patient reaches the adolescent period.

The case presented here is classified as the lateral or alternating type according to Hinman's[23] simplified grouping of three types of true hermaphroditism; they are:

1. *Bilateral:* testis and ovary on both sides, either separate or united as an ovotestis.
2. *Unilateral:* testis and ovary, either separate or united, on one side, with testis or ovary on the other.
3. *Lateral or Alternating:* testis on one side and ovary on the other.

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CASE REPORT

History.—R. T., a 15-year-old Negro, was admitted to the Le Bonheur Children's Hospital on Jan. 23, 1956, because of enlargement of the breasts and abnormalities of the external genitalia.

The patient was born as the result of a normal pregnancy of a para iii gravida iv mother with an apparently uncomplicated delivery. At the time of birth, it was noted that the infant had ambiguous external genitalia which prevented definite assignment of sex. The infant was taken to a local physician soon after birth for a physical examination. Determination of chromosomal patterns was not available at that time. Since the genitalia resembled that of a male more than that of a female, the baby was given the name Robert and reared as a male. The patient remained quite healthy, at no time had signs or symptoms of electrolyte imbalance or other abnormalities, and grew and developed with a normal male physique.

At 6 years of age, the child started to school and was accepted as a male. Participating in sports and with male companionship, social adaptation was adequate throughout the childhood period.

At 12 years of age a definite deepening of the voice was apparent, erections of the small phallus were experienced, and sexual drives were oriented toward the female.

At 13 years of age, a routine blood examination by the Public Health Department revealed a positive test for syphilis and the patient was given antisyphilitic treatment. It was also during the thirteenth year that bilateral enlargement of the breasts was noted. The breasts continued to enlarge to a size that caused embarrassment to the patient. There was no history of bleeding from the perineal opening or abdominal cramping indicative of menarche.

The patient had 9 siblings, all of whom were well and had no apparent abnormalities.

Physical Examination.—The patient appeared to be a well-nourished and well-developed Negro boy measuring 5 feet and 9 inches in height (Fig. 1). The temperature, pulse, and blood pressure were normal. There was no beard visible. The thyroid was not enlarged to palpation. The breasts were enlarged bilaterally to the size of those of a 17- or 18-year-old girl and mammary ducts were palpated radiating from the nipples. No abnormalities of the heart and lungs were found.

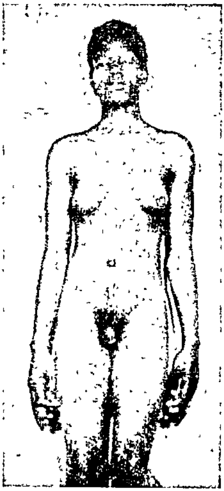

Fig. 1—Anterior view of patient revealing bilateral breast enlargement characteristic of a female with body build and external genitalia resembling a male.

The liver, spleen, and kidneys were not enlarged and no abnormal masses were found by abdominal palpation. A small amount of fine axillary hair was present. Pubic hair was present but did not extend onto the abdominal wall to a level that would permit the classification of male distribution. The phallus was 4 cm. in length with a well-defined glans and a perineal hypospadias was equally visible (Fig. 2). A firm, movable mass, 2 cm. in diameter, was palpable near the external inguinal ring in the right scrotal sac which resembled the labium majus. A defect in the left inguinal ring permitted a small herniation, but no gonad could be palpated in the left labium. No prostate or cervix could be palpated through the rectum.

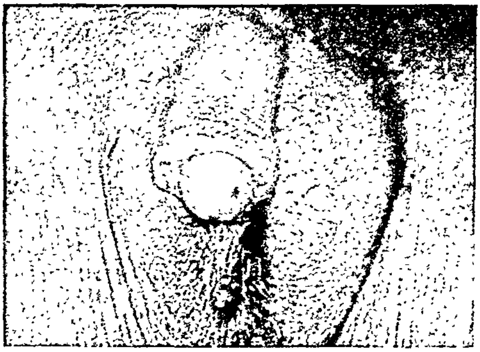

Fig. 2.—Close-up view of external genitalia illustrating small phallus, hypospadic urethra, and labia resembling scrotum.

Laboratory Findings.—The urinary excretion of 17-ketosteroids in 24 hours was 4.9 mg. (Table I). Serum chloride was 108 mEq. per liter; NPN was 31 mg. per 100 c.c.; and a VDRL test was positive, 1:2 dilution.

Pyelograms and Osseus Development.—No abnormalities were apparent on the intravenous pyelogram or plain roentgenogram of the abdomen. Osseous development was normal for the patient's age. Chest and skull roentgenograms were not abnormal.

Endoscopy and Biopsy.—At endoscopy, the apparent urinary meatus in the perineum was found to be a common channel, and, about 2 cm. from the external orifice, there was a urethral orifice leading into a normal bladder. The channel extended posteriorly and superiorly into a blind pouch interpreted as vagina. In the most distant portion of the pouch, a small dimple could be seen which might have been a hypoplastic cervical os. On completion of the inspection, a vaginogram was made which outlined the vaginal pouch described.

Exploration of the right labium exposed a pearly white mass, approximately 1.5 cm. in diameter. The capsule of this oval nodule was incised with removal of a biopsy section for frozen section examination. The soft orange-tinted gray tissue underlying the firm outer covering had a stringy structure resembling testicular tissue.

Microscopic examination of the biopsy removed from this labial mass identified the structure to be atrophic testicular tissue (Fig. 3). Beneath the fibrous capsule the cross sections of seminiferous tubules typically appeared in islands or groups in a loose connective tissue stroma (Fig. 3). Interstitial cells in the loose stroma did not appear to be abnormal but appeared to be decreased in number. Evidence of spermatogenesis was absent; spermatogenic cells were not observed.

Adjacent to the testicular mass in the right labium was a smaller elongated structure with a passage extending from this toward the inguinal canal, but without a demonstrable communication into the abdominal cavity. Histologic study of the second mass proved this to be epididymis of essentially normal architecture (Fig. 4).

A large left inguinal hernia was present, but no masses or nodules were found in the left inguinal canal.

The hernial sac was opened and the adjacent peritoneal cavity was explored with a finger. A small, round mass was outlined, but its identity and anatomical attachments could not be established.

Exploratory Laparotomy.—On Feb. 2, 1956, an exploratory laparotomy was performed by Dr. George Livermore, Jr., and revealed a hypoplastic uterus, a grossly normal left Fallopian tube, and a mass resembling a left ovary in normal relation to the tube and uterus. Frozen section examination of the gonadal mass showed the

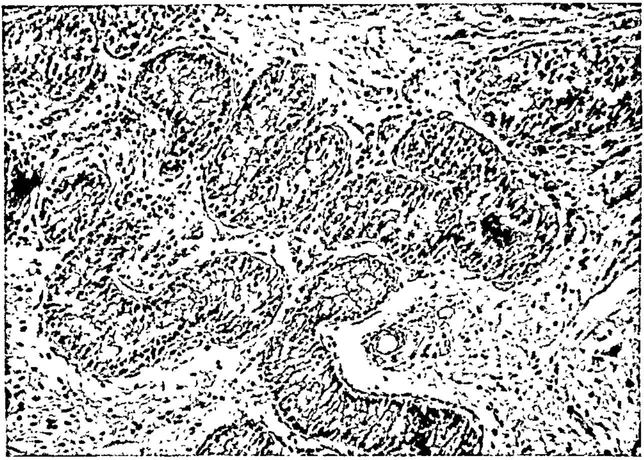

Fig. 3.—Biopsy section of atrophic testicular tissue from mass of right labium majus. The cells within the prominent basement membrane of the seminiferous tubules appear to be only of Sertoli type. (Hematoxylin and eosin; ×100; reduced ¼.)

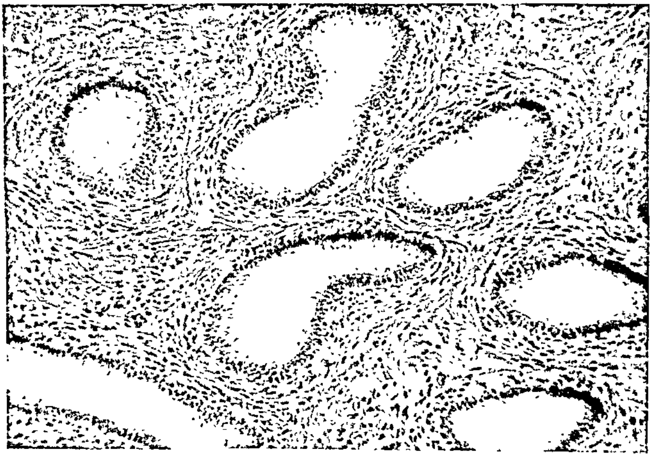

Fig. 4.—From right labial mass adjacent to testis. Normal epididymis. (Hematoxylin and eosin; ×100; reduced ¼.)

wedge biopsy to be tissue of ovarian structure. No other internal genital organs or masses were found; the uterus, left Fallopian tube and left ovary were removed (Fig. 5).

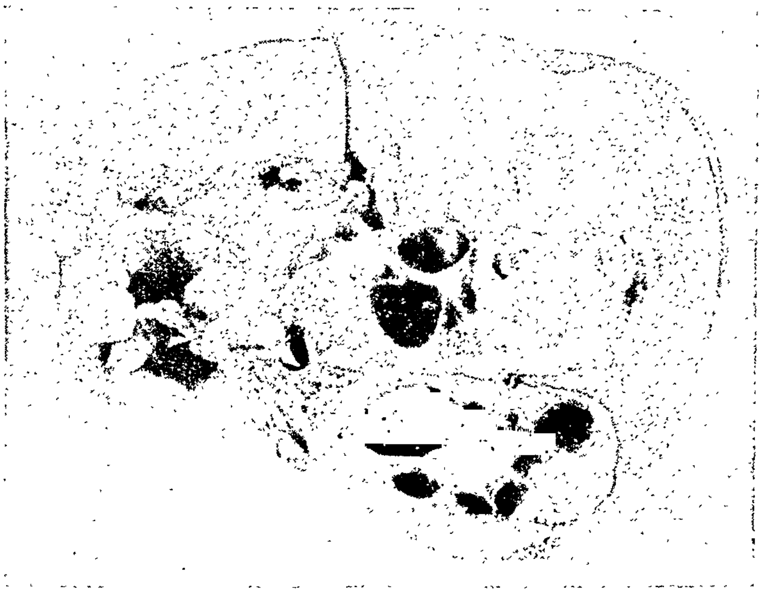

Fig. 5.—Uterus, left tube, and left ovary, posterior view; uterine mass to right with left tube extending superiorly from left cornua to the free fimbriated end. The ovary has been hemisected to show the multiple large hemorrhagic follicular cysts.

Pathologic examination of uterus, left tube, and ovary: The bean-shaped uterus measured 5 by 2 by 2 cm., and on section had a small, poorly defined endometrial cavity. The dimpling of the blunt cervical end of the uterus did not communicate with the endometrial cavity. In the microscopic sections of the uterine wall, the estrogenic proliferative type endometrium is of especial interest. There is some variation in size and shape of columnar cell-lined endometrial glands, a few enlarged irregular cystic glands, and small polypoid projections into the endometrial cavity. The latter hyperplastic cystic changes are moderate (Fig. 6).

The Fallopian tube measured 8 cm. in length and was grossly and histologically normal.

The ovary measuring 3 by 2 by 2 cm. contained many thin-walled cysts measuring up to 1 cm. in diameter. The thin fluid contents and lining walls of larger cysts were uniformly hemorrhagic as illustrated in Fig. 5. The microscopic examination revealed a thick, dense, fibrous capsule without covering germinal epithelium. The cortex is made up of characteristic but fibrous ovarian stroma containing but few structures resembling primordial follicles. The greater portion of the ovary as illustrated (Fig. 5) is occupied by the large hemorrhagic follicular cysts. The larger follicular cysts are lined by thin or single layer of cuboidal granulosa or by fibrous-appearing theca; these cysts uniformly had prominent perifollicular hemorrhage with blood in adjacent stroma. Several small peripheral cysts in the cortex (Fig. 7) are lined by granulosa, several cells in thickness with rosette-like pattern and as in the follicle illustrated with peninsula-like accumulation of granulosa cells. Other small atretic follicles are lined by hyalinized compressed connective tissue cells and contain blood. Of interest are the

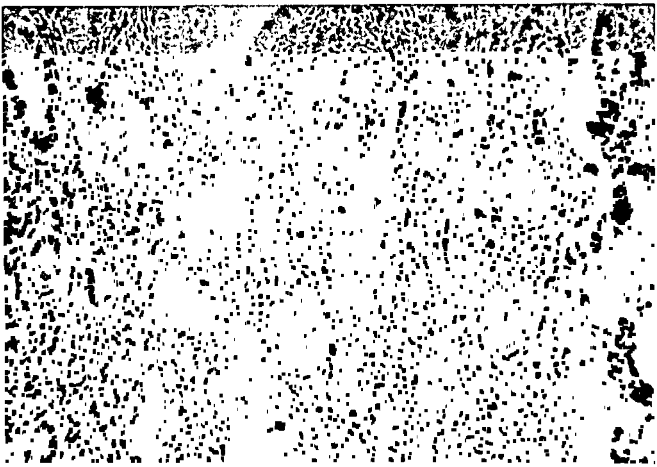

Fig. 6.—Proliferative endometrium. The endometrial cavity and surface epithelium is at the *right*. (Hematoxylin and eosin; ×100; reduced ¼.) A portion of one of large irregular cystic glands is shown at the *top* margin.

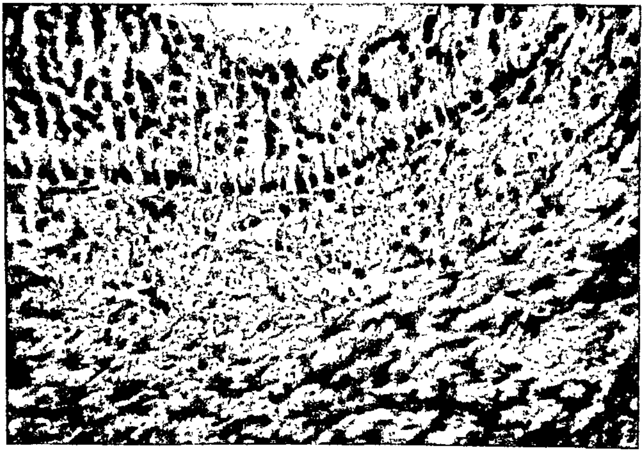

Fig. 7.—Section of ovary. Granulosa cell lining adjacent to cumulus-like prominence of cystic follicle. Multicelled granulosa lining present only in few of smaller peripheral cystic follicles. (Hematoxylin and eosin; ×200; reduced ¼.)

many very small double-layered wavy hyalinized structures considered to be remnants of obliterated atretic follicles.

Sex-chromatin studies: Skin specimens were examined from the left groin, right thigh, and left subscapular region for the nuclear sex chromosomal pattern by the method described by Moore, Graham, and Barr.[2] The nuclear chromatin masses described as typical of the sex chromatin pattern of female cells were not found in the skin from the several sites described. These examinations were considered as evidence indicating these specimens represented the male chromosomal pattern. Biopsy sites from the various quadrants of the body were chosen to test the possibility that one area might contain a male pattern and another the female. This was not found to be true.

Hormone studies: Unfortunately, complete hormonal studies were not obtained preoperatively; however, 4 months after removal of the ovary, the urinary excretion of follicle-stimulating hormone level was 110 mouse units per 24 hours.

TABLE I. TWENTY-FOUR-HOUR URINARY EXCRETION OF FOLLICULAR-STIMULATING HORMONE AND 17-KETOSTEROID

	FSH (MOUSE UNITS)	17-KETOSTEROID (MG.)
Preoperative		4.9
Postoperative		
4 mo.	110	
8 mo.	110	12.6
12 mo.	105	7.0

Eight months after this surgical procedure, the urinary 17-ketosteroid excretion was 12.6 mg. per day, and the follicle-stimulating hormone was still 110 mouse units. One year following the oophorectomy, the 17-ketosteroid content of the urine was 7.0 mg. in a 24-hour specimen and the follicle-stimulating hormone was 105 mouse units.

Before surgery the 17-ketosteroid excretion was 4.9 mg. per day. The ovary apparently was functioning, as evidenced by breast enlargement prior to oophorectomy and by the rather high follicle-stimulating hormone excretion during the postoperative period. An alternate explanation of the increase in FSH is a low androgen output of testicular origin during the postoperative period. A 17-ketosteroid output of 12 and 7 mg. per 24 hours in the postoperative period may be accounted for by adrenal androgen output.

Two months following hysterectomy, a bilateral mammoplasty was performed. Over an 8-month period, a 3-stage repair of the hypospadias was undertaken, producing a penile urethra. The vaginal cavity was not removed. No hormone therapy was deemed necessary.

According to the recommendation of Wilkins[25] and Money[26] and their coworkers, we can assume that serious psychologic complications were avoided through rearing this patient consistently as a boy, leaving no doubts as to his assignment to the male sex. When his breasts started to enlarge at the age of 12, his gender role was already firmly imprinted. The danger of changing the original decision as to assignment of sex in later childhood has been stressed recently by the above authors.

SUMMARY

1. A case of true hermaphroditism of the lateral type is presented in which a cystic atrophic ovary was found in the left adnexa, a normal left Fallopian tube, a small uterus, and an atrophic testis in the right side of a bifid scrotum.

2. Skin specimens from various portions of the body each revealed a male chromosomal pattern.

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JACKSONIAN SEIZURES IN INFANCY AND CHILDHOOD

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FROM 1934 to 1954 inclusive, 66 patients were admitted to the St. Louis Children's Hospital with the chief complaint of local motor or jacksonian convulsions. Another 48 with similar seizures were registered in the Pediatric Convulsive Clinic over a 5-year period from 1950 to 1955. A study of these 114 cases of jacksonian epilepsy in infants and children forms the substance of this paper.

Incidence.—The 48 out-patient cases were culled from a list of 637 consecutive cases of epilepsy of diverse types —an incidence of 1:13 or 7.5 per cent. The real frequency is probably higher. Generalized seizures not observed from the onset may have a focal origin (particularly true with nocturnal attacks) or local discharges may spread so quickly as to appear bilateral clinically. Patients reported to have generalized seizures, but with greater involvement on one side, were not included in this study.

Sex and Race Distribution.—In our series, 60 patients were boys and 54 were girls.

Only 1 (0.6 per cent) of the hospital patients and 10 (20.8 per cent) of the clinic group were Negroes. Since about 10 per cent of the hospital population and one half of our clinic patients are Negro, in both instances the ratio of Negro to white patients is far below average.

A study of the literature on racial distribution of epilepsy revealed contradictions and no unequivocal preponderance.

Age at Onset of Seizures.—Fig. 1 shows the age at onset of seizures. The range is from birth to 15 years with a maximum incidence in the first 2 years of life. Almost one half of the cases, 48 per cent, occurred before 3 years of age. Save for a secondary peak at 8 years of age, there is a progressive decrease in incidence from birth to adolescence. We believe this early onset of jacksonian seizures in children reflects etiological factors such as congenital cerebral defect, birth injury, and hereditary tendency.

No unusual association is apparent for the relatively high incidence at 8 years of age; 2 followed head injury, 1 was a patient with congenital hemiplegia, another gave a history of neonatal respiratory embarrassment, and 1 was a patient who several years previously had had encephalitis with neurological residuals; in the remaining 8 cases no etiology was manifest.

Of interest is the frequency of a long interval between cerebral involvement and the residual epilepsy. In 17 cases of hemiplegia evident within the first 2½ years of life, seizures on

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the paretic side began after the age of 4½ years in 7 cases (respectively at 4½, 5, 5½, 6, 6, 8, and 11½ years of age). In a case of "spontaneous subarachnoid hemorrhage" at 3 months of age, jacksonian seizures began 4 years later. One patient developed recurrent jacksonian epilepsy 6 years after an apparent recovery from head injury associated with a depressed skull fracture. During the acute phase of the injury the child had had several jacksonian seizures.

Walker[1] states, "The convulsions in posttraumatic epilepsy usually begin within 2 years of the cerebral injury; *if a longer latent period exists,* the possibility of some other etiological factor is enhanced." Our findings in the above and other instances demonstrate that a delayed onset of organic epilepsy is not exceptional in children. This confirms Penfield and Jasper's[2] impression of a delayed onset of posttraumatic epilepsy in childhood.

Family History of Epilepsy.—In 19 cases there was either no mention of a family history of epilepsy or it was unknown, uncertain, or distant. In the remaining 95 cases, the family history was positive in 27 cases (28 per cent). In one half of these, epilepsy was present in either the parents (10 cases) or siblings (4 cases). Seizures occurred in more than one member of the family in 4 cases.

Lennox[3] has reported the incidence of epilepsy among relatives of patients with organic seizures to be three times that of the general population. Other authors, Penfield and Jasper,[2] Ziskind and Ziskind[4] and, recently, Walker[1] have not been able to confirm this association. However, in a personal communication to Penfield and Erickson,[5] Lennox later stated that "when the symptomatic group of epilepsies is subdivided there is evidence of inheritance of the condition among those whose seizures begin early in life following trauma, while adult epileptics with brain tumors or traumata show no greater incidence of epileptic relatives than do a group of normal control persons." The extraordinary incidence of epilepsy in the close relatives of our young patients with jacksonian epilepsy confirms Lennox's observations.

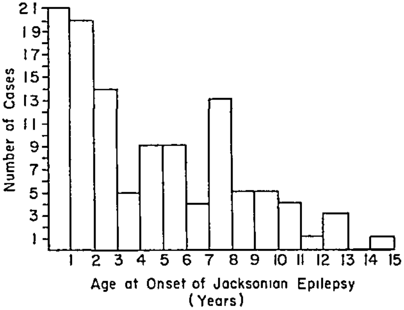

Fig. 1.

ETIOLOGY OF JACKSONIAN SEIZURES

Jacksonian seizures imply local organic pathology. Nevertheless, a definite cause for the convulsions could be determined in only 39 cases or 34 per cent (Table I). The early age of onset of seizures suggests prenatal and paranatal factors as the most common cause of jacksonian epilepsy in childhood. The fact that 61 per cent of the cases with known etiology are on such a basis strengthens this impression. An uneventful delivery does not exclude birth injury. Keith and Norval[6] studied 57 infants with neurological lesions apparent during the first 2 weeks of life. Of 18 neonatal deaths, 6 had intracranial hemorrhage without history of a difficult delivery.

Birth Injury.—Thirteen patients (11 per cent) had a history of difficult delivery with neonatal asphyxia. Several others with prolonged or complicated deliveries were not included because of the lack of unequivocal signs or symptoms of brain damage in the baby.

TABLE I. JACKSONIAN SEIZURES

ETIOLOGY	NUMBER OF CASES
Birth injury	12
Birth injury plus ganglioneuroma	1
Infantile hemiplegia	11
Acquired CNS disease	11
? Acquired CNS disease	1
? Secondary to febrile seizures	1
Telangiectasis of cerebral cortex	2
Unknown	75

Type of delivery was mentioned in 9 of the 13 cases: one was by Caesarean section, 4 were spontaneous, 2 were vertex presentations with forceps application (one high), 1 was a footling breech with forceps, and another was a spontaneous breech with the umbilical cord wrapped around the neck. Four mothers in this group were eclamptic at the time of delivery —in 2, their infants were premature (1,830 grams and 2,310 grams). The smaller premature had congenital cataracts without mental retardation.

Two of the 13 patients (15.3 per cent) gave a family history of epilepsy.

Five of the group (38.4 per cent) had a hemiplegia detected before they had learned to walk.

Four patients had convulsions in the neonatal period. The nature of these was clear in only 1 case (jacksonian). Residual jacksonian seizures developed before 18 months of age in only 5 cases. In the remaining 8 patients, the age at onset ranged from 4 to 8 years. Seizures appeared after 6 years of age in 4 patients (30.7 per cent). As noted before, this delayed onset of epilepsy following brain injury in infancy differs from adult experience.

Infantile Hemiplegia.—Eleven patients without history of neonatal difficulty or subsequently acquired illness or injury had hemiplegias detected early in infancy (before 1 year of age in 6 cases and after 18 months in only one). One infant was premature (1,890 grams). There was a family history of epilepsy in 4 of these cases (36.3 per cent).

The age at onset of jacksonian seizures ranged from 6 months to 11½ years; 5 cases before 2½ years and 6, slightly more than 50 per cent, after 5½ years of age. Again we have evidence of delayed onset of residual epilepsy after cerebral injury.

Three patients had other convulsions prior to the onset of jacksonian epilepsy. Respectively, these were febrile, grand mal, and massive myoclonic seizures.

Acquired Disease of the Central Nervous System.—Eleven patients had postnatally acquired central nervous system disease.

Symptomatic skull fractures were responsible for 3 cases. Another head injury with a large open wound was included. Seizures occurred within 6 weeks of the accident. Since head injury is so common in children, in the above case, as in several others not included in this study, the head injury may have been coincidental. There was 1 case of encephalitis (type undetermined). Two cases were due to bacterial meningitis and 2 followed spontaneous subarachnoid hemorrhage. One patient had seizures on the basis of hypertensive encephalopathy of acute glomerulonephritis. The course of events in another patient—ruptured appendix, pelvic and abdominal abscesses, bacteremia, empyema, and then sudden onset of jacksonian seizures with hemiparesis suggested intracranial embolus or thrombosis.

Two other cases deserve comment. One had grand mal seizures during the course of malaria. Later she exhibited psychomotor and jacksonian seizures. Cerebral complications in malaria are recognized and may have been responsible for the seizures or they could be classified as simple febrile seizures. In the other case, illness was ushered in by generalized febrile convulsions and hemiparesis; coma persisted for 1 week. No systemic or central nervous system disease could be found. In infants and young children, very high fever associated with uncontrolled seizures has been known to cause brain damage.[7] Under such circumstances, one cannot exclude the possibility that subsequent seizures are a residual of such injury.

Excluding the above 2 cases, 8 of the 11 patients had hemiplegia evident at the onset of their injury or illness. This was transient in 3 and permanent in the remainder.

Two of the head injury cases had jacksonian seizures only during the acute stage of increased intracranial pressure. One of these developed temporal lobe epilepsy later. The patient with hemiparesis following a ruptured appendix had jacksonian seizures from the onset of illness. The remaining 8 patients developed or had recurrent jacksonian seizures from 4 weeks to 6 years after the primary disease (over 4 years in 3 cases). Occasionally other types of seizures occurred prior to the onset of jacksonian epilepsy. This was the case in the patients with meningitis and encephalitis.

Seven patients in this group (63.6 per cent) had more than one type of seizure. These were mostly of temporal lobe origin but grand mal with and without fever and myoclonic petit mal were also seen.

None of these patients with postnatally acquired brain disease gave a family history of epilepsy.

Space-taking Pathology.—Jacksonian seizures are invariably regarded with more concern than generalized convulsions. Of foremost concern is the possibility of a cerebral space-taking lesion. Considering the urgency of early diagnosis of brain tumor such an association may be warranted in adults but rarely so in infants and children. Intracranial tumor is seldom the cause of jacksonian epilepsy in the pediatric age group. In a series of over 800 children with focal discharging lesions of the brain studied by

Kellaway,[8] the incidence of neoplastic lesions was less than 2 per cent. We do not perform routine air encephalograms in cases of focal epilepsy in children unless there is evidence of increased intracranial pressure, neurological deficits or if the patient fails to respond to adequate anticonvulsant therapy. Livingston[9] also lists these indications for pneumoencephalography in patients with focal clinical seizures. Considering that such criteria may not present at the onset of focal seizures all of these patients must be examined at regular intervals to exclude a progressive organic lesion.

In the present series of 114 cases of jacksonian epilepsy, brain tumor was found in only one patient and was not necessarily related to the jacksonian seizures. This child sustained severe birth injury; ". . . the doctors thought they would never get him to cry and that he would die." From the age of one month to one year, he had daily jacksonian seizures. From 5 months to 3 years of age he also had daily akinetic or myoclonic seizures. Permanent hemiparesis was obvious early in life. Subsequent studies revealed a large ganglioneuroma in the region of the septum pellucidum and cortical sclerosis. It is tempting to consider the jacksonian seizures related to the atrophic cortical lesion and the akinetic seizures to the midline neoplastic lesion.

Diffuse surface hemangiomas were demonstrated in 2 cases. In 1, jacksonian seizures began at 4 months of age. There was right hemiparesis and mental retardation (IQ 41). At 6½ years of age she was referred here for study. X-rays revealed intracranial calcification in the left posterior parietal region. At surgery, a large venous hemangioma was found extending from the posterior part of the left parietal lobe to the Sylvian fissure and medially to the falx. In the other patient, jacksonian seizures began at 10½ years of age. Craniotomy revealed telangiectasis of the motor cortex paramedially.

CLINICAL ANALYSIS OF SEIZURES

About 20 per cent of the patients exhibited seizures of diverse types. This number does not include febrile convulsions, either generalized (6 cases) or focal (6 cases). Such evidence suggests diffuse rather than local brain dysfunction. Radiological and psychological findings support this impression. Five patients had grand mal epilepsy, 5 had myoclonic or akinetic seizures, 9 had classical temporal lobe seizures, and in 6 others the seizures are best described as "equivalents" (paroxysmal coma, headaches, abdominal pain). Four patients in the series had two or more different types of seizures besides their jacksonian ones.

Jacksonian Seizures.—Of the 114 cases of jacksonian epilepsy, 59 occurred on the right side and 51 on the left. In 3 instances, seizures occurred on either side on different occasions and in one case the parents were not certain which side was involved.

In only 60 cases was the exact site of origin mentioned. Most commonly the seizures started in the face (25 cases); 8 of these originated at the corner of the eye, 5 at the mouth. The remaining 12 were not localized further. Seventeen began in the "hand." The "arm" was mentioned as the primary site of involvement in

7 cases and the "shoulder" in 2. In only 9 cases did the seizures begin in the lower extremity; 6 in the "leg" and 3 in the "foot."

Thirty patients gave a history of abnormal sensation prior to movement in the part first involved. This was described as "pins and needles," "tingling," "numbness," "stinging," "warm" or "hot," "asleep" and "funny." Two patients experienced pain at the onset. Two had weakness or paralysis preceding the unilateral clonic convulsion. Four patients had visual auras—blindness, blurring of vision, or seeing colored lights. Frequently seizures consisted only of these sensory symptoms. Undoubtedly a higher percentage of patients had sensory aura than is reported here since this was not specifically asked for in the history. Furthermore, a good proportion of our patients were too young to express such feelings. Correctly speaking these are somatosensory or visual seizures with spread of neuronal discharge to the pre-Rolandic area.

Nocturnal jacksonian episodes are common. In the clinic group of 49 patients, 9 had jacksonian seizures only during sleep and in another case all seizures but one were nocturnal.

"Febrile" Seizures.—A considerable number of those having "febrile seizures" in infancy later have seizures without fever. These may be of any type. Six of our series had generalized seizures associated with fever prior to the onset of jacksonian epilepsy. In 4 of the 6, febrile seizures occurred on many occasions before the first jacksonian convulsion. In these cases one considers hereditary predisposition, undetected CNS disease at the time of the first febrile seizure, and the possibility of focal organic residual from the febrile episode itself.

In patients with febrile seizures there frequently is a high incidence of similar episodes in near relatives. Three of the 6 cases had a family history of convulsions, in 1 case the mother, in another the father, and in the third a first cousin.

In none of these 6 cases did the history suggest central nervous system disease responsible for the febrile seizures. Most often the febrile seizures were associated with respiratory infection and less frequently with gastrointestinal disturbances. In 1 case, the first seizure occurred at 19 months of age during an attack of "mumps." There was no clinical evidence of meningoencephalitis and subsequently this child had many febrile seizures before the onset of afebrile jacksonian seizures at age 3 years.

The age at onset of these "febrile seizures" was 5 months, 8 months, 10 months, 17 months, 3½ years, and 5 years, respectively. Except for the latter this age distribution is characteristic of febrile seizures.

In these 6 cases, jacksonian epilepsy appeared 6 months, 2 years, 2½ years, 3½ years, 8 years, and 12½ years individually after the febrile episodes. In one instance even the jacksonian seizures first occurred with fever. In the others the jacksonian seizures were *afebrile*. Subsequent to febrile convulsions in infancy, one patient later had repeated grand mal seizures without fever for several years before the onset of jacksonian epilepsy.

Electroencephalograms taken in every instance after the onset of jacksonian seizures were focal in 3 of the

6 cases. Two showed slow dysrhythmias and another had a paroxysmal nonfocal record.

Only 1 of these patients was mentally retarded. The mother had eclampsia at the time of delivery and there was severe neonatal asphyxia. Several febrile seizures associated with upper respiratory infections occurred at 3½ years of age. The jacksonian seizures began at age 6.

In 2 cases discussed in the section on etiology, we could not exclude the possibility that the first febrile seizure was on a basis of disease of the central nervous system. For this reason these are not included here.

Febrile Jacksonian Seizures.—Six patients had their first jacksonian seizure during an acute febrile illness or infection without fever (one case). Again these usually were uncomplicated upper respiratory infections and occasionally gastrointestinal.

Brain damage, evident for months or years before the onset of seizures in 3 of these cases supports our contention that fever and infection act as a trigger mechanism in precipitating latent jacksonian epilepsy. One of these children had meningitis in the first week of life. Subsequently she showed microcephaly with motor and mental retardation. At 16 months she developed jacksonian seizures. At first these occurred only with fever. Another patient with congenital left hemiparesis developed left jacksonian seizures at 2½ years of age. These were seen only with fever for several years before they occurred spontaneously. The third patient had a history of a difficult instrumental delivery and neonatal anoxia. Hemiparesis was detected in infancy. Frequent afebrile jacksonian seizures began at the age of one month. Later he had both generalized and unilateral seizures associated with febrile illness.

On follow-up, 5 of the 6 patients later had nonfebrile jacksonian seizures or continued to have both febrile and afebrile local seizures off and on for years.

To emphasize this relationship between fever and seizures, other observations deserve mention. One patient whose early seizures were jacksonian without fever later had such seizures precipitated by febrile illness. Two patients subject to both febrile and nonfebrile unilateral seizures had on different occasions generalized "febrile seizures." It appears that not only can patients with simple febrile seizures later have jacksonian seizures without fever but also that fever and/or infection can precipitate a latent trend for jacksonian epilepsy. The situation is analogous to the adult with grand mal epilepsy who, during childhood, had such seizures only with fever. Furthermore, patients with jacksonian epilepsy may exhibit generalized seizures at the time of febrile illness.

In sharp contract with the group who had generalized convulsions associated with fever prior to the onset of jacksonian epilepsy none gave a history of familial epilepsy.

Electroencephalograms were focal in 5 cases; 3 were paroxysmal focal and 2 showed a slow focal pattern. The sixth showed a nonfocal paroxysmal slow dysrhythmia.

Grand Mal Seizures.—In 37 cases the jacksonian seizures spread to the other side in a generalized convulsion on one or more occasions.

Five patients were reported to have had primary grand mal seizures. In 3 infants, the jacksonian seizures followed several months of generalized seizures. It is possible that in these cases a focal origin may have been unobserved. However, in at least 2 cases, it appears that bilateral seizures preceded the onset of jacksonian epilepsy. One child with congenital hemiparesis had many grand mal seizures from age 11 months to 6 years. At this time he developed focal seizures on the paretic side. The other child had a febrile seizure when 17 months old. At 20 months of age, she had her first afebrile seizure. From then until age 4 years she had repeated grand mal seizures without fever. At 5 years of age she first began having frequent jacksonian seizures.

Petit Mal Variants.—Only the clinical impression of atypical petit mal attacks is implied; the electroencephalograms did not necessarily conform with what is called *petit mal variant.*

Five patients had "atypical" petit mal of the akinetic or massive myoclonic type. Clinically, it is difficult to distinguish the two seizures. Since the distinction is questioned,[10] we have grouped the two together. No patient exhibited classical petit mal (simple staring).

Age at onset of these seizures in the 5 patients was 5 months, 17 months, 18 months, 2½ years, and 4½ years, individually.

None had a family history of epilepsy.

In only 1 case did the jacksonian seizures precede the atypical petit mal and it is possible that they were unrelated in etiology. This infant had a history of severe neonatal anoxia with congenital right hemiparesis and right jacksonian seizures since the age of 1 month. At 5 months of age he developed akinetic seizures ("slumping spells"). Surgical exploration revealed temporal lobe sclerosis and a large central ganglioneuroma. In the other 4 cases, jacksonian seizures occurred 1 month, 6 months, 2½ years, and 3½ years after the onset of the petit mal-like seizures.

There was clinical evidence of organic brain involvement in every case. One had severe microcephaly and another congenital hemiparesis. One patient developed akinetic petit mal 3 months following an illness with severe febrile seizures, prolonged coma, and hemiparesis. The fifth patient had encephalitis at 2½ years of age, with residual hemiparesis and mental retardation. At age 4½ years she began to have masticatory seizures and myoclonic spasms. At age 8 years, 5½ years after the original illness, she developed repeated jacksonian seizures.

Three of these 5 patients were grossly retarded, 1 questionably so and not determined in the other.

Other Seizures.—Nine patients had seizures suggesting temporal lobe origin—vertiginous aura, mastication, hyperacusis, manifestations of terror, and hallucinations. Frequently these were more disabling or caused greater concern than the jacksonian seizures.

Three patients had "syncopal epilepsy"—attacks of coma preceded by vague aura and followed by postictal phenomena (drowsiness, vomiting, headache).

Two had "cephalic epilepsy"—paroxysmal headaches suggestive of epileptic discharge.

One patient suffered recurrent attacks of abdominal pain consistent with the diagnosis of "abdominal epilepsy."

HEMIPLEGIA

Congenital and Acquired Hemiplegia.—Twenty-seven of the 114 patients (23.6 per cent) had hemiplegia. In 3 cases, due respectively to meningitis, hypertensive encephalopathy, and skull fracture, the hemiparesis improved. In the others it was permanent.

Etiology is listed in Table II. Fifty-nine per cent were congenital or due to birth injury.

Reference to a family history of epilepsy was made in 24 of the 27 cases. It was positive in 4. This incidence is only one half of that for the entire series.

TABLE II. HEMIPLEGIA (27 CASES)

ETIOLOGY	NUMBER OF CASES
Birth injury	5
Congenital	11
Hemangioma	1
Meningitis	2
Subarachnoid hemorrhage	1
Encephalitis	1
Embolus or thrombosis	1
Hypertension	1
Malaria	1
Fever of unknown origin	1
Head injury	2

Pneumoencephalography was performed in 13 cases. Abnormal findings were found in 10 (76 per cent).

Thirteen, or 48 per cent, of these patients showed degrees of mental retardation.

Postepileptic Hemiplegia.—Following local motor seizures, transitory paralysis is usual. Bravais[11] first described this phenomena in his thesis "l'epilepsie hemiplegique." Todd and Robertson[11] are credited for the hypothesis that this paralysis depends on temporary ganglionic exhaustion consequent to excessive discharge during the paroxysm. Apparently Hughlings Jackson[11] had independently arrived at a similar conclusion. Excluding the 27 cases of congenital or acquired organic hemiplegias, 40 of the remaining 87 patients in the series had a history of postictal paralysis of varied duration. The true incidence is undoubtedly higher. Minimal weakness may easily go unnoticed in an infant or young child and too often this information was not ascertained.

Jackson[11] states, "Nerve fibres being only exhausted, and not destroyed, as in some other kinds of paralysis, post-epileptiform paralysis is temporary, unless, of course, the fit recurs soon." Of particular interest to us were several patients in whom such paralysis became permanent. From 16 cases of permanent postictal paralysis, 10 have been selected. In the remaining 6, the follow-up period was too short or the circumstances such that other etiology was possible although unlikely. In all of the cases there was no apparent etiology; seizures occurring in healthy children without fever, dehydration, or other signs and symptoms.

Since recovery can occur over a period of weeks or months, prolonged observation is necessary before one can conclude that paralysis is permanent. All of the cases were followed for at least 1 year after the onset of a seemingly permanent residual; 5 have been followed from 5 to 21 years.

Seven of the 10 patients were 3 years of age or younger when their seizures began. This is probably significant. The immature brain is believed more liable to extended postictal depression and to brain damage from repeated or prolonged seizures.

Residual weakness became apparent from as early as a few hours to as late as 7 years after onset of seizures. In the latter case a change of handedness several years before suggests an earlier onset of permanent paresis. With each seizure the duration of the Todd's paresis was variable but with a progressive degree of permanent disability.

In every case the attacks were of extreme frequency or prolonged duration or both. In 4, the jacksonian seizures occurred from one to hundreds daily and for a period ranging from 5 to 12 years in 3 of these 4. Two patients averaged seizures at least once a week for 2½ and 12 years, respectively. Seizures occurred at least once a month for 1 year in 1 patient and for 11 years in another. Frequent seizures were generally of short duration (less than one minute).

Four patients in this group showed abnormalities by ventriculography. Case 10 had been virtually in a state of "epilepsia partialis continua" for over 1 year, yet ventriculograms and arteriograms were normal. In Case 6, death from unrelated causes permitted examination of the brain. The left cerebral hemisphere was larger than the right with prominent sulci. There was moderate dilatation of the left lateral ventricle. Microscopic studies revealed no right-left difference in the cerebral cortex.

At the time of the last observation 9 patients were still having recurrent seizures.

Penfield and Jasper[2] cite several examples of postictal paralysis progressing in severity with each attack and with advancing cortical destruction. In addition to the metabolic disturbances concomitant with epileptic discharge, they considered the vascular changes observed during and after discharge of the exposed epileptic cortex as significant in the production of such paralysis.

The frequency of occurrence of progressive increase in the degree and duration of motor paralysis following jacksonian seizures, particularly in children, points clearly to the need for prompt recognition and treatment.

MENTAL RETARDATION

Evidence of mental deficiency was present *prior* to the onset of jacksonian seizures in 28 cases (24 per cent). Considering the nature and circumstances of these seizures, this incidence is not high. In the follow-up survey, 4 others were reported to have developed mental retardation consequent to recurrent convulsions. Serious behavior disorders were exhibited by 4—1 of these is included in the group with acquired mental retardation.

Twelve of these 28 cases had psychometric evaluation. Seven had IQ's of less than 50. In the remaining cases, mental retardation was apparent from the history and by examination.

Organic etiology or neurological abnormality was present in 19 of these 28 cases (67 per cent). These are listed in Table III.

Despite the severity of the neonatal distress only 7 of the 13 patients with recognized birth injury showed mental deficiency. The degree of retardation was questionable, mild or moderate in 6 cases and severe in only one.

Only 4 of the 11 patients with "congenital" infantile hemiplegia exhibited mental retardation.

Residual mental and motor retardation was seen in 3 cases following infections of the central nervous system (viral, bacterial, and parasitic).

Other recognized causes for mental defect were head injury in 1 case and diffuse cerebral hemangioma in another. Three patients had microcephalus or hydrocephalus of undetermined cause.

The high incidence of other types of seizures in these patients suggests diffuse brain damage. Twelve had "atypical" petit mal, grand mal, focal and generalized febrile convulsions or temporal lobe seizures, as well as jacksonian epilepsy.

TABLE III. MENTAL RETARDATION

ETIOLOGY	NUMBER OF CASES
Birth injury	7 (3 with hemiplegia)
CNS infection (viral, bacterial, parasitic)	3
Head injury	1
Hemangioma	1
Microcephaly	1
Congenital hemiplegia	4
Hydrocephalus	2
Unknown	9

Air encephalography was performed in 15 cases. Ten, 66 per cent, showed gross abnormalities; 5 were considered normal. One patient with a normal verticulogram demonstrated a large superficial venous hemangioma by arteriography.

Three of the 4 patients with acquired retardation had pneumoencephalograms with abnormalities seen in only one.

The 4 patients with serious behavior disorders had neither known cause for the seizures nor neurological deficits. Pneumoencephalography was performed in 1 case with normal findings.

THE ELECTROENCEPHALOGRAM

Properly used, the term *jacksonian seizure* connotes a discrete origin of convulsive discharge in the surface cortex of the opposite central region of the brain, the discharge spreading from the point of origin to become generalized. Using the plan of cerebral localization, the site of origin of a focal seizure can be inferred from the history, the signal symptom (that part where the first contraction or sensation occurs) being the important localizing event. If that signal symptom relates to the foot, the hand, or the corner of the mouth or eye, a further localization along the central gyri is permissible. Thus, face, hand, and foot signals implicate, respectively, the opposite Sylvian, intermediate and vertex parts of the central gyri.

Brain wave tracings are ordinarily obtained in free periods between seizures, and the following impressions are important in considering the data to be presented. With optimal electroencephalogram recording, it is ordinarily possible to detect even a quite circumscribed epileptogenic lesion and prove its position later by electrocorticography at operation. However, particularly in children, the scalp recording of a unique focal transient during an interseizure period may only signify an underlying focus of high excitability within a much larger area of disturbed functioning. Such a focus might be indistinguishable from one which relates to a discrete underlying epileptogenic lesion. Thus, only by correlating the electroencephalogram findings with other neurological lateralizing signs, and with evidence from pneumoencephalography and arteriography, can we impute a site of structural disorder to a particular focal pattern. A focal spike, then, points only to the epicentre of a convulsive disturbance, and this discrete area of highest excitability may be presumed to trigger both the signal symptom of the clinical seizure and the spikes which are recorded during seizure-free intervals. Our experience with follow-up air studies in such cases, and less often with arteriograms, leads us to believe that the focal spikes which signify only a pathophysiological process significantly outnumber those in which a structural lesion can be imputed by other procedures as well.

Other impressions also aid in evaluating the findings in the present study. In serial tracings, each obtained in a seizure-free interval, a spike focus may be present on one occasion, absent on another. Thus, in dealing with a doubtful history of jacksonian seizures a single negative tracing will not rule out a focal origin for the convulsive process. Again, separate spike foci may appear in some cases, one related to each hemisphere. Both are not necessarily evident in the same tracing, and this may account for the instances in which a single record suggests the neurological paradox of a spike focus over the hemisphere ipsilateral to the seizure's initial manifestation. Generalized spiking can also occur in interseizure tracings from cases classified on clinical grounds as jacksonian. Even so, the repetitive spike discharge which develops at the onset of a clinical seizure in such a case differs qualitatively as well as quantitatively from the sporadic single spikes of generalized distribution recorded during interseizure intervals. Thus, the seizure discharge itself may have a discrete origin even though interseizure spiking is generalized.

There are also cases of jacksonian seizure in which spikes do not occur in interseizure periods, slow foci appearing instead. Compared with spike foci, slow focal patterns are more likely to relate closely to the suspected site of origin, and if they occur invariably at the same site in serial tracings are clearly suspicious of an underlying structural lesion. Again, only a generalized disturbance of rhythm, usually slow, may characterize the tracing in a jacksonian case, or the frequency of the interseizure tracing may even be quite normal. These variants are mentioned because even in the absence of interseizure evidence of a focus a convulsive tendency may still express itself at intervals.

The wide range of normal variability in the infant's electroencephalogram and the difficulty in securing artifact-free records makes the interpretation of focal changes more difficult than in older children and adults. In neonatal life, the subcortical centers mature more rapidly than does the cerebral cortex, and it is the electrical activity of the later maturing cortex which is expressed primarily in the electroencephalogram. Experimental evidence also indicates that it is more difficult for the immature cortex to synchronize a spike discharge. Even considering these difficulties, focal spikes can sometimes be recorded surprisingly early in neonatal life (6 days in our experience); but in infants negative evidence has much less significance than in older children. Thus, if there is a strong suspicion of a focal convulsive process it is wise to repeat the tracing at intervals.

Prolonged postictal slowing of the young child's electroencephalogram is another factor which complicates the interpretation of the supposed jacksonian seizure tracing. A record made a few hours after either a focal or a generalized seizure may show markedly slow activity, and even asymmetry in amplitude between the traces from the two hemispheres to suggest a focal process. The same child, recorded during a seizure-free interval, may show a tracing which is much better ordered. Thus, it is advisable to repeat all tracings done in the postictal period to appraise the interval character of the electroencephalogram.

In evaluating the electroencephalogram of the present series of cases, the interval frequency pattern was classified: (1) as within the limits of variability of the normal for that age; (2) as mildly slow representing an equivocal departure from the normal; (3) as intermediate slow; and (4) as markedly slow. In occasional tracings, fast activity was intermingled with intermediate or markedly slow activity; these were classified as mixed fast and slow. Convulsoid transients were considered apart from the resting frequency, all highly synchronized transients of unique form being classified as spikes. Finally, slow patterns which appeared consistently at one lead were classified as slow foci.

Of 83 children in the series who had electroencephalograms, 18 had neurological lateralizing signs leading to the presumption that structural abnormality involved a part or all of one hemisphere. Of that 18, only 3 (from the out-patient series) showed resting frequencies that could be considered normal, and all of them showed focal or generalized intermittent spiking. In all other tracings from this group, the resting frequency showed intermediate or markedly slow departure from the normal. Of the 18 cases, 10 presented focal spiking over the central region of the suspected hemisphere, and in 3 others spikes of generalized distribution were recorded. In only 1, was the focal spike process recorded from the nonsuspect hemisphere. There were also 2 slow wave foci detected over the central region of the suspected hemisphere. The remaining 2 showed only an intermediate or markedly slow disorder of the usual resting rhythm. Thus, in 12 of the 18 cases a focal process was recorded in the expected locale.

Of the 65 cases without evidence of neurological abnormality, 17 or one fourth showed a normal resting frequency. Of the 17, 5 showed focal spikes at the suspected site and 6 generalized or at least nonfocal spiking. The resting frequency of the remainder was classified as intermediate or markedly slow. Of the total cases without neurological abnormality, 19 showed focal spike processes where it was suspected that they might occur, but in 6 others the focus was paradoxical, appearing over the nonsuspect hemisphere. In one of the latter group, ventriculograms were done and proved to be normal. There were also 15 cases which showed generalized spiking. Slow focal patterns were recorded in 7 of the group and all occurred over the central region of the suspected hemisphere. Of the remainder, 1 showed a completely normal tracing and the others only intermediate or markedly slow resting frequencies without focalization.

The chronological span was 5½ months to 14 years. Disregarding coincident neurological abnormality for the moment and rating only on the basis of success in recording a focal process of 12 children under 2 years of age, 5 had spike foci over the suspected hemisphere and in 5 others the localization was equivocal, nonfocal, or paradoxical; 2 showed no spikes at all. Compared with the cases over 2 years, the expectancy for obtaining a consistent localization was significantly lower.

We conclude that the expectancy for recording a focal pattern over the suspected hemisphere in a jacksonian seizure case increases with age and also with the coexistence of other evidence of neurological abnormality. However, focal processes are not of themselves pathognomonic of an epileptogenic lesion, for our results indicate that the number of cases with focal disorder in which no other neurological abnormality could be found was significantly larger than the group in which a neurological abnormality could be proved to coexist.

AIR ENCEPHALOGRAMS

Adequate air encephalograms by the spinal subarachnoid route or by ventricular punctures were made in 47 cases. Only one half were considered abnormal.

Six of the 13 cases with recognized birth injury had air studies. Abnormalities were demonstrated in all but one. Two had moderate bilateral symmetrical ventricular dilatation. One showed atrophy of the right cranium with dilatation of the corresponding ventricle. In another there was unilateral ventricular dilatation with a mild degree of porencephaly, cysts communicating with the anterior part of the body and anterior horn of the lateral ventricle. The fifth case had suprasellar calcification. At ventriculography, a calcified tumor was seen in the left lateral ventricle infiltrating the septum and pushing it to the right. At surgery this patient had two lesions—cortical sclerosis in the side opposite the hemiplegia and a benign ganglioneuroma attached to the septum pellucidum and extending into the lateral ventricle.

Pneumoencephalography was performed in 7 of the 11 patients with congenital hemiplegia. Five showed abnormalities. Two had relatively localized lesions, 1 a minimal cortical atrophy of the left frontoparietal region (right hemiplegia) and the other a porencephaly in the left frontoparietal region (right hemiplegia). In 2 cases, there was a unilateral dilatation of the ventricular system with a shift to the side opposite the hemiplegia. One patient showed bilateral cortical atrophy, greater on the side opposite the hemiplegia.

Only 3 of the 13 patients with postnatally acquired central nervous system disease had air studies. Clinically, each exhibited hemiparesis and pneumoencephalograms revealed contralateral ventricular dilatation.

In the remaining 11 cases with abnormal pneumoencephalographic findings, no etiology was apparent. Six had symmetrical dilatation and in the remainder there was unilateral ventricular dilatation.

Ten of the 24 patients with gross pneumoencephalographic abnormalities were retarded mentally by clinical or psychometric evaluation. Another who early exhibited only a severe personality defect, when seen 6 years later, during which time he continued to have seizures, appeared unquestionably mentally retarded.

Since space-taking lesions, neoplastic or otherwise, are rarely the cause of jacksonian seizures in infants and children it has been our policy to postpone air encephalography unless there is evidence of increased intracranial pressure, neurological deficit, or a failure of response to adequate anticonvulsive therapy.

In the infant, subdural taps are recommended to exclude subdural hematoma. These are more essential than air studies. We have seen several cases of large bilateral subdural hematoma in which pneumoencephalograms were normal. On the other hand, angiography, when correctly performed, will rule out a subdural hematoma.

Cerebral arteriograms were made in 6 cases with abnormal findings in only 1. Two of the 5 patients with negative arteriograms showed abnormalities by pneumoencephalography. On the other hand, the 1 patient who showed abnormal arteriograms had normal ventriculograms.

SUMMARY

One-hundred and fourteen cases of jacksonian epilepsy in infants and children are reviewed.

Incidence.—The reported frequency of local motor seizures, 7.5 per cent is probably too low because of failure of observation from onset or rapid spread of epileptic discharge.

Sex.—Both sexes were about equally affected.

Race.—The ratio of Negro to white patients was considerably below the hospital average.

Age At Onset.—The greatest incidence was among infants and young children with a progressive decline toward adolescense. Forty-eight per cent were less then 3 years of age. It seems logical to implicate pre-, peri-, and postnatal factors in etiology.

A delayed onset of organic epilepsy was usual.

Heredity.—Twenty-eight per cent of 95 cases had a history of epilepsy in close relatives (half in parents or siblings). This confirms Lennox's impression of the influence of heredity in organic epilepsy in children.

Etiology.—Cause was known in only 34 per cent of cases. Almost two thirds were related to birth injury (13 cases) or congenital or infantile hemiplegia (11 cases). Eleven patients had postnatal acquired disease of the central nervous system of varied etiology. Diffuse surface hemangiomata were demonstrated in 2 cases. Only one patient had an expanding intracranial lesion. The latter also had severe birth injury with hemiplegia and extensive cortical sclerosis. Cerebral neoplasm is a relatively rare cause of jacksonian epilepsy in infants and children.

Seizure Analysis.—There was no right or left predominance of jacksonian phenomena. One third had bilateral spread. The commonest site of origin was the face or hand. Only 9 of 60 cases began in the leg. Abnormal sensation prior to movement was common. Nocturnal attacks were fairly frequent.

Six patients had febrile seizures before the onset of jacksonian epilepsy. In 4 these were of great frequency. The interval between the febrile and jacksonian seizures was over 2 years in 5 of the 6 cases. One half of this group had a family history of epilepsy. Occasionally, circumstances suggested that jacksonian epilepsy might be a residual of local brain damage from severe and protracted seizures with high fever.

In another 6 cases, early jacksonian seizures occurred only with fever and infection. The presence of severe neurological abnormalities prior to the onset of seizures in 3 of these cases confirms the impression that fever and infection can trigger a latent tendency for jacksonian epilepsy.

Twenty-five patients had other types of seizures. Five had *grand mal* epilepsy prior to the onset of local seizures. Five with organic brain involvement had "atypical" petit mal (myoclonic or akinetic). In 4, these preceded the onset of jacksonian epilepsy. Fifteen patients had recurrent paroxysmal phenomena compatible with epileptic discharge without motor component.

Hemiplegia.—Twenty-seven patients (23.6 per cent) had hemiplegia. The majority were attributable to prenatal factors or birth injury. Forty-eight per cent were mentally retarded. Post-epileptiform paralysis (Todd and Robertson) of varied duration was common. With frequently recurring or prolonged seizures such paralysis may be progressive and ultimately permanent. This was the case in at least 10 patients in our series. This course of events attests to the need for prompt control of jacksonian seizures.

Mental Retardation.—Twenty-eight patients (24 per cent) were mentally retarded prior to onset of jacksonian epilepsy. Etiological factors were evident in two thirds. Four patients appeared to develop mental retardation consequent to severe recurrent seizures. Serious behavior disorder was a chief complaint in 4 children.

The Electroencephalogram.—In general, the conformance of focal electroencephalogram findings with inferences drawn from pattern of seizure is good, even when only a single tracing is available. An expected electrographic focus is more likely to be demonstrated in a child than in an infant. Spike foci are nonspecific indicators of a region of high cortical excitability, and not necessarily of underlying structural abnormality. Slow wave foci, recorded with or without accompanying focal spike discharges, more frequently presage proof of underlying structural disorder.

Of the 83 children in the series who had electroencephalograms, 18 had neurological lateralizing signs. In 12 of these, a focal process was recorded in the expected locale. In the remaining 65 cases without neurological abnormality, 19 showed focal spike processes in the suspected hemisphere and in 6 others the focus was paradoxical. Fifteen showed generalized spiking. Seven showed slow focal patterns over the central region of the suspected hemisphere. One tracing was normal and the remainder showed intermediate or markedly slow resting frequencies without focalization.

Air Encephalograms.—Close observation of patients with local seizures is essential. Encephalography is not routine. Criteria for air studies are increased intracranial pressure, neurological abnormalities or failure of response to adequate antiepileptic therapy. One half of the encephalograms made were considered abnormal. Recognized cause for these abnormalities was present in only 13 of 24 cases. Ten of the 24 patients with abnormal air studies were retarded mentally. Arteriograms were sometimes abnormal with normal pneumoencephalograms and vice versa.

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Accidental Deaths in Infancy

Infants found dead in bed, are not generally killed by being lain on by their mothers, but by being suffocated under the bed-clothes, with carbonic acid gas exhaled from their own lungs and re-inspired. They die without pain, in a profound sleep. Mothers, give your babes more air. Let them sleep with their heads uncovered. Do not let them go to sleep on or under your arm, for when you cover yourselves, in the half unconsciousness of partial sleep, you will cover your darlings' heads also, and in the morning may find them still in sleep—a sleep from which your caresses cannot awake them.

FROM THE PACIFIC MED. AND SURG. JOURNAL, 1858.

VOMITING IN INFANCY AND EARLY CHILDHOOD: TREATMENT WITH PROCHLORPERAZINE

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PROMPT treatment of physical disorders in children is often seriously impeded by the presence of persistent vomiting. Not only does vomiting interfere with the oral administration of medication at home, but it also, by dehydration, lowers the child's capacity to withstand physical disease. The need to check vomiting, therefore, may often become imperative.

In recent years the antiemetic activity of a number of phenothiazine derivatives has been studied.[1-3] Among the newest of these derivatives is prochlorperazine (Compazine*), which has been reportedly effective as an antiemetic in adults.[4, 5] The drug also functions as a tranquilizer.[6, 7]

Recently, prochlorperazine became available in syrup form for investigational use in pediatrics. The authors undertook to evaluate prochlorperazine for the efficacy of its antiemetic activity and its suitability for pediatric practice.

METHOD

The 44 children selected for this study ranged in age from 4 months to 9 years. All of them had suffered three or more vomiting episodes daily. Symptoms of one or more of the following conditions were present in 36 patients: acute gastroenteritis, measles, mumps encephalitis, diarrhea, acute pharyngitis, acute nasopharyngitis, pertussis, acute glomerular nephritis, acute tonsillitis, streptococcal pharyngitis, and atherostomatis. Vomiting had persisted, sporadically, from 18 hours to 3 days prior to treatment with prochlorperazine. In the other eight patients, in addition to vomiting, one or more of the following symptoms were seen: nervousness, overactivity, insomnia, abdominal pain of unknown origin, eye blinking, and facial grimacing. These eight patients had been vomiting sporadically for 7 to 10 days before treatment began. The patient with abdominal pain showed no evidence of intestinal obstruction or other pathological conditions.

Doses were graduated from 2.5 mg. (or ½ teaspoonful) three times a day for the youngest patients, to 5 mg. four times a day for the oldest patients. Concomitant with the administration of the antiemetic, therapy directed to the underlying condition was given to 18 patients. This concomitant therapy included diet restriction, antibiotics in cases with bacterial infection, and intravenous fluids for dehydration. There was no concomitant therapy for any of the psychically disturbed patients.

In evaluating the efficacy of the drug, promptness of antiemetic action

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*Smith Kline & French Laboratories.

was considered of prime importance. A patient whose vomiting abated after the first or second dose was considered to have made an excellent response. Abatement of vomiting within twelve hours, or a single, mild vomiting episode following an excellent response, was rated good. A reduction in the number of episodes of vomiting was rated fair. Anything else was considered poor. Abatement of vomiting was considered achieved when oral fluids and medication were retained. Naturally, other factors—side effects and acceptability of the medication to the patients—were also considered in evaluating the responses.

RESULTS

Of the 36 patients whose vomiting was associated with organic disease, 14 had an excellent response, vomiting abating after the second dose in almost every case. A good response was seen in 19 patients, a fair response in 1 patient; 2 patients showed no appreciable improvement. Thus, 92 per cent of these young patients were free of vomiting—and were able to retain fluids and medication—within a twelve-hour period; that is, after three or, in a few cases, four doses.

Those patients whose vomiting had persisted for less than 36 hours before onset of medication had a higher percentage of excellent responses than those patients whose vomiting had persisted for more than 36 hours. The medication seemed to be as effective in the infants as in the older children. Of the 8 children in the study who were less than 1 year old, 7 were free of vomiting within twelve hours. Of the 8 patients whose vomiting was associated with psychic disturbance, 3 had a good response to prochlorperazine, 1 a fair response, and 4 did not show any appreciable improvement.

In neither group of patients were there any observable side effects. No patient manifested jaundice, abnormal urinary findings, or change in white or red count. The patients' parents reported, in most cases, that the fruit-flavored syrup was acceptable to the children, and that resistance to second and third doses was either less than to initial doses or was absent entirely.

DISCUSSION

Although the group of patients is relatively small, we were pleasantly surprised by the fact that 92 per cent of these patients showed a marked improvement in vomiting in 12 hours or less. Since antibiotics frequently induce vomiting, prochlorperazine faced a particularly significant test in 7 children who received concomitant antibiotic therapy. Yet, 5 of these patients were free of vomiting within 6 hours, and all 7 were relieved of vomiting within twelve hours.

Although half of the psychically disturbed children responded favorably to the antiemetic, it must be borne in mind that psychic disorders frequently require extensive and prolonged treatment. It is of interest, however, that the use of prochlorperazine as an antiemetic in these psychically disturbed children was in no case attended by the side effects frequently associated with certain other antiemetic therapies. Our past experience with barbiturates in the treatment of emotionally induced vomiting, for example, is similar to Gatski's,[8] who found that barbiturates tend to make disturbed children inaccessible even to superficial psychotherapy and, in some cases, actually excite the child further.

Although there were no observable side effects, it must be kept in mind that many of these very young patients are quite inarticulate and are therefore unable to communicate their subjective reactions clearly. Nevertheless, the writers received the distinct impression that prochlorperazine caused little, if any, discomfort and distress among the children in the study. The patients seemed quieter, though not sedated, and less apprehensive of pain. Whether these desirable effects were due to the tranquilizing action of prochlorperazine and/or the drug's prompt antiemetic activity is difficult to tell.

Since antiemetic drugs may mask acute surgical conditions, they must be used cautiously in pediatric practice, and only after examination and diagnoses have excluded such conditions as appendicitis. This caution is particularly apt in respect to prochlorperazine because of its effectiveness and promptness in controlling vomiting.

Prochlorperazine demonstrated low dosage requirements. Its administration was safe and uneventful when given to patients as young as 4 months of age.

SUMMARY

Prochlorperazine was given as an antiemetic to 36 young children suffering from persistent vomiting associated with physical diseases, and to 8 children suffering from persistent vomiting associated with emotional disturbance.

Of the children whose vomiting accompanied physical disease, 92 per cent were relieved of vomiting within twelve hours after the initial dose of prochlorperazine or after a total of three doses. Of the children whose vomiting was associated with emotional disturbance, 50 per cent were relieved of vomiting episodes in the twelve-hour period. Prochlorperazine also seemed to exert a tranquilizing effect on the patients, for they seemed less restless and apprehensive. There were no observable side effects.

Prochlorperazine was found to be an effective and safe antiemetic for pediatric practice.

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TRANSPLACENTAL PASSAGE OF THE L. E. FACTOR

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In 1954, Bridge and Foley[1] demonstrated the L. E. cell in the cord blood and bone marrow of a newly born baby of a mother with disseminated lupus erythematosus. Brief mention was made of another mother with this disease, where again the L. E. cell was demonstrated in the cord blood of her offspring. The authors believed that placental transmission of the L. E. factor had occurred. In 1957, Berlyne, Short, and Vickers[2] reported two more mothers with disseminated lupus erythematosus who gave birth to babies in whose peripheral blood L. E. cells were seen. Transplacental passage of the L. E. factor was also thought to have occurred in these instances.

We wish to report a fifth case of probable placental transmission of the L. E. factor from mother to baby. In our case, the mother also had established disseminated lupus erythematosus and L. E. cells were repeatedly demonstrated in the peripheral blood of her baby.

CASE REPORT

The mother was a 22-year-old white girl who was in good health until the age of 15 years when she was found to have idiopathic thrombocytopenic purpura; a splenectomy was performed after which she had a complete recovery. She remained well until her first pregnancy at the age of 20 years. After three months' gestation she developed migratory arthralgia, recurrent fever, general malaise, and intermittent rash on the lower extremities. Repeated bone marrow and peripheral blood examinations demonstrated the L. E. phenomenon. She delivered a viable male infant after thirty-five weeks' gestation. The infant died within 24 hours. Clinical features and autopsy findings were consistent with the diagnosis of "hyaline membrane disease." The placenta was normal on gross and microscopic examination.

Two months after her first pregnancy the patient was started on cortisone, 100 mg., which she received for one year when it was changed to Meticorten, 25 mg. daily. The patient did very well and Meticorten was gradually decreased to 10 mg. daily.

The second pregnancy was uncomplicated. The patient remained on Meticorten throughout her pregnancy. After nine months' gestation, there was a normal low forceps delivery (Dec. 6, 1956). The placenta was normal on gross and microscopic examination. Laboratory studies done on the mother's blood on the day of delivery revealed a hemoglobin of 15.0 Gm. per 100 c.c. of blood; the hematocrit was 46 per cent; L. E. examination (nonclotted method) on the peripheral blood was positive; blood group A, Rh negative; serologic test for syphilis was negative. Urinalysis revealed 2+ albuminuria with occasional red blood cells per high-power field (*centrifuged* specimen). Post-partum course of the mother was uneventful.

The baby was a normal female. The weight was 6 pounds 1 ounce and the

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length was nineteen inches. Blood group was A, Rh positive. The cord bilirubin was 0.3 mg. per cent direct and 3.0 mg. per cent indirect. The Coombs' test (direct and indirect) was negative. The hemoglobin was 20 Gm. per cent and the hematocrit 60 per cent. There were normoblasts, 1,800 per cubic millimeter. During the second day of life, the baby was reported to be dusky on several occasions; she vomited several times. At the age of 20 hours, an L. E. preparation was done on the peripheral blood of the baby (nonclotted method) and found to be positive (Fig. 1). During the third day of the baby's life she continued to vomit. The cord was noted to be foul smelling and was removed. Cultures of the blood and umbilical cord stump were obtained, and the patient was started on penicillin and streptomycin. Blood chemistries that day revealed sodium of 145 mEq. per liter, chloride of 107 mEq. per liter, and potassium of 5.9 mEq. per liter. The white blood cell count was 16,600 with 66 per cent neutrophils, 29 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophils. On the fourth day of life the child was noted to be jaundiced. Serum bilirubin (age 90 hours) revealed a total of 15 mg. per cent with an indirect value of 14.55 mg. per cent.

Subsequent specimens drawn at the age of 102 hours showed a serum bilirubin of 18.0 mg. per cent with an indirect value of 17.4 mg. per cent. Repeated L. E. preparations which were done daily during her hospitalizations were all found to be markedly positive. However, no rosette formation was noted. Electrophoretic protein pattern obtained at the age of 5 days revealed albumin, 4.221 Gm. per cent, and globulin: alpha I, 0.297 Gm. per cent; alpha II, 0.416 Gm. per cent; beta, 0.654 Gm. per cent; and gamma, 0.862 Gm. per cent. Serum complement determination done on the same blood specimen[3] showed a level of 9.5 U. 50 per cent (U. 50 per cent is used

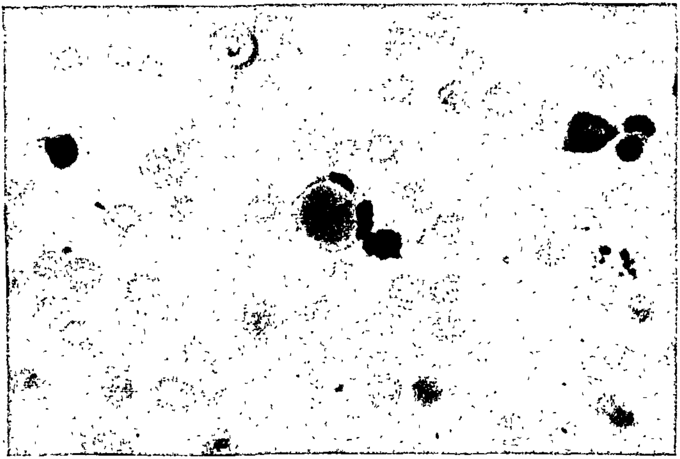

Fig. 1.—L. E. cell in infant's peripheral blood.

to indicate 50 per cent hemolytic units per milliliter of undiluted serum).

After the fifth day of life the child did very well. She stopped vomiting, and the jaundice disappeared. Blood culture and throat culture (obtained shortly after birth) showed no growth. Culture from the umbilical cord stump grew out *Staphylococcus aureus*. Chest roentgenograms taken on the third and fifth days of life were within normal limits. The baby was discharged eight days after birth in good condition.

During her hospitalization and subsequent to her discharge the baby was fed by bottle, since the mother did not have any breast milk.

The baby was followed in the Outpatient Department where repeated L. E. examinations were found to be positive on weekly examination up to the age of 7 weeks; however, during the last three weeks it had been very hard to find any L. E. cells and the ones which were noted were of poor quality. Three biweekly L. E. preparations after the seventh week were negative. No rosettes were seen at any time. The baby was last seen at the age of 8 months, at which time she showed excellent growth and development.

DISCUSSION

In the case described by Bridge and Foley and the cases described by Berlyne, Short, and Vickers, the L. E. cell could still be demonstrated in the peripheral blood of the baby at the age of 7 weeks but not beyond that age. In our case, similarly, the L. E. cell was not present after the age of 7 weeks.

The duration of the L. E. phenomenon corresponds roughly to the half-life of gamma globulin and appears to support the conclusion of passive transfer of the L. E. factor[1] (the L. E. factor being a component of the gamma globulin fraction as shown by Haserick[4]).

Glagov and Gechman[5] speculated upon the possible relationship of transplacental L. E. factor passage and the familial occurrence of disseminated lupus erythematosus. They suggested possible concomitant transplacental transmission of antigenic substances provoking antibody formation and eventually an anaphylactic sensitivity or, perhaps, the L. E. factor itself being transmitted and sensitizing the fetus to some unknown antigen.

If the presence of the L. E. factor in the offspring of a patient with disseminated lupus erythematosus during the newborn period is more than just passive transfer and perhaps a subclinical immunological manifestation, one might expect a depressed serum complement level.

The serum complement level at the age of 5 days was 9.5 U. 50 per cent (measurement of 50 per cent hemolytic units per milliliter of undiluted serum). Ten normal infants were tested, all at the age of 5 days, and found to have serum complement levels ranging from 8.58 to 33.90 U. 50 per cent (mean 17.43 U. 50 per cent).* Serum complement level in our patient at the age of 3 months was 18.0 U. 50 per cent and at 6 months was 33.5 U. 50 per cent. Very few data exist on serum complement levels during the newborn period; the levels which have been reported show a wide range.[6, 7] The serum complement level of our patient, although low at the age of 5 days, appears to fall within the normal range. Conclusions from a single case would be premature. In this instance, however, there is no evidence to suggest a hypersensitivity phenomenon immediately after birth.

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*Method as described in Pediatrics 11: 570, 1953, by Janeway and Wedgwood, except that cell suspension was adjusted by method of Kent, Bukantz, and associates, using the formula $V_2 = \frac{V_1 O_1 D}{0.500}$.

SUMMARY

A case of transplacental transmission of the L. E. factor is presented. Serum complement and gamma globulin levels in the offspring were within normal range.

We wish to thank Dr. Jack E. Githens, Associate Professor of Pediatrics, University of Colorado, for reading the manuscript and Master Specialist L. B. Nolte, USA Research and Development Unit, Fitzsimons Army Hospital, for technical assistance.

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Multiple Births

How Many Children Can a Woman Bear?—Dr. Szukits says that this question has not yet been satisfactorily answered. He himself has observed two females, each of whom had borne twenty-four children. Osiander (*Handb. d. Entbindungs Kunst*, 1 Theil, 1 Abth. S. 319) mentions one woman who during her married life bore 44 children, and another who had 53. Burdach (*die Physiol. als Erfahrungswissenschaft*, 1 Bd. 1826, S 410) relates that the wife of a countryman in the Moscow district had given birth to 69 children at 27 confinements—four times four at one birth, seven times three, sixteen times twins. In the year 1809, the Vienna newspapers contained the following announcement: Maria Anna Helm, the wife of a poor linen weaver in Neulerchenfeld, 20 years married, bore at 11 confinements 32 children; 28 living, and 4 dead: 26 were males, and 6 females; all were begotten by one man, and nursed by herself.

Six children seem to be the largest number ever produced at one birth. A perfectly trustworthy instance of this is the following: The *Schwäb. Mercur*, 1805.—The wife of a chimney-sweep here, named "Düpfer," was yesterday confined of six children; all were boys, and dead. This woman, who has been twice married, has already given birth to 44 children. During her first marriage, which lasted twenty-two years, she bore 27 boys and 3 girls. In her second marriage, which has lasted but three years, she has born 14 children—3 at the first, 5 at the second, and now 6 at third confinement (Osiander, 320).

ED. MED. JOURN., JUNE, 1858, FROM ZEITSCHRIFT, d. K. K. GESELLSCHAFT D. AERZTE ZU WIEN, JULY AND AUGUST, 1857.

UNEXPLAINED DEATH FROM EXCHANGE TRANSFUSION

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During the 11 years that have elapsed since the introduction of exchange transfusion for the treatment of hemolytic disease of the newborn, attention has been periodically focused on the fact that this procedure is not without its dangers and may occasionally be associated with unexpected fatality. Allen and Diamond[1] have recently pointed out that, with few exceptions, it has been impossible to explain the deaths that arise during or shortly after exchange transfusion. Walker and Mollison[2] have listed the causes of death occurring in association with hemolytic disease of the newborn in England and Wales during the years 1953 and 1955. In 88 (16 per cent) of 550 deaths, the fatality arose during or within 4 hours of exchange transfusion. The immediate cause of death was not apparent in these cases but, from the clinical information available, it seemed that death should not otherwise have taken place at that time.

The following case reports are presented in the belief that they represent a sequence of events which must occur in a certain but at present unknown proportion of sudden deaths arising during exchange transfusion.

CASE REPORTS

Case 1.—*Cardiac Arrest During Exchange Transfusion.*—

This female infant was delivered by cesarean section on the tenth of September, 1957. Cesarean section was performed at 35 weeks' gestation because of a rise in maternal D antibody titer to 1/32, and because of the death of the 3 preceding siblings from hemolytic disease. The infant weighed 2,220 Gm. She cried spontaneously and on examination appeared normal except for yellow staining of the vernix and the umbilical cord. The spleen was not palpable. The cord blood serum bilirubin was 6.4 mg. per cent, hemoglobin 9.5 Gm. per cent, hematocrit 26 per cent, and reticulocyte count 14.4 per cent. The direct Coombs' test was positive.

The first exchange transfusion was carried out within one hour of delivery. Using a 10 c.c. syringe, 415 c.c. of blood were withdrawn and 384 c.c. of packed cells injected. Throughout the 1-hour procedure the infant's condition remained satisfactory. Following the exchange, the serum bilirubin was 2.5 mg. per cent, the hemoglobin 13.4 Gm. per cent, and the hematocrit 35 per cent.

At the age of 7 hours, the serum bilirubin had risen to 9.0 mg. per cent and a second exchange transfusion was given. Using the same technique as before, 310 c.c. of blood were withdrawn and 290 c.c. injected in less than 1 hour. The infant's condition remained satisfactory throughout and periodic electrocardiographic (ECG) tracings taken with a direct writing

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Sanborn electrocardiograph revealed no abnormalities in the standard leads. A few minutes after the exchange had been completed the infant developed a generalized convulsion which responded to intramuscular injection of 2 c.c. calcium glucoheptonate. During the next few hours, a few petechial hemorrhages developed on the skin of the face and trunk.

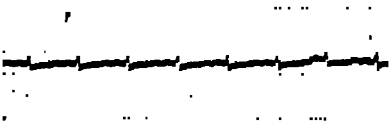
Fig. 1.—Case 1. Lead I. Time from start of exchange—17 min.; volume of blood injected—30 c.c.; normal nodal rhythm, rate—135 per minute.

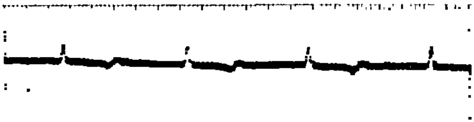
Fig. 2.—Case 1. Lead I. Time from start of exchange—28 min.; volume of blood injected—70 c.c.; slow nodal rhythm, rate—53 per minute.

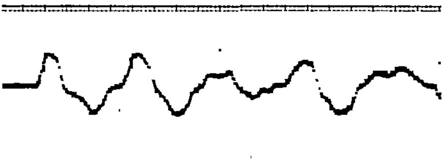
Fig. 3.—Case 1. Lead I. Time from start to exchange—30½ min. Ventricular fibrillation

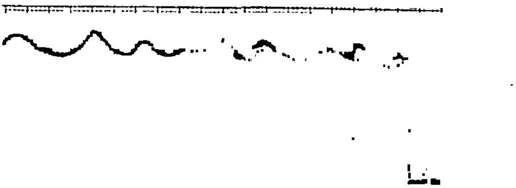
Fig. 4.—Case 1. Lead I. Time from start of exchange—32 min. Cardiac arrest.

At the age of 22 hours, the serum bilirubin was 13.6 mg. per cent, the hemoglobin 8.3 Gm. per cent, and the hematocrit 21 per cent. A third exchange was attempted using 7-day-old blood which had been packed by removal of supernatant plasma a few hours before the exchange. After 80 c.c. of blood had been withdrawn and 70 c.c. injected, an ECG tracing taken

28 minutes after the commencement of the exchange showed evidence of slow nodal rhythm. (Figs. 1, 2, 3, and 4.) During the next 4 minutes, the cardiac slowing progressed to ventricular fibrillation and complete cardiac arrest. At the time of detection of the cardiac slowing the infant's condition appeared satisfactory. There were no signs of respiratory distress, cyanosis, or pulmonary adventitious sounds. Clinical signs of collapse were only apparent when the ECG tracing showed evidence of ventricular fibrillation. The cardiac arrhythmia was uninfluenced by discontinuing the exchange and immediate injection of 2 c.c. calcium glucoheptonate into the umbilical vein. The heart remained in asystole for a period of 5 minutes, but responded to intracardiac injection of Adrenalin, and artificial respiration with tracheal intubation and intermittent positive pressure oxygen.

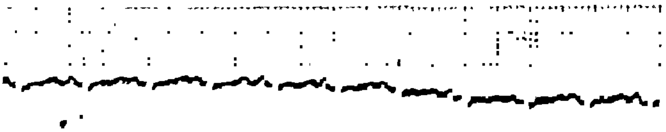

Fig. 5.—Case 2. Lead I. Time from start of exchange—27 min.; volume of blood injected—80 c.c.; normal nodal rhythm, rate—156 per minute.

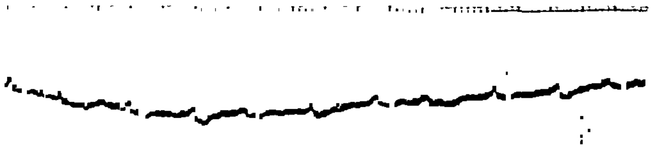

Fig. 6.—Case 2. Lead I. Time from start of exchange—27 min.; volume of blood injected—185 c.c.; slow nodal rhythm, rate—80 per minute.

For the remaining 14 hours of her life the infant remained in a precarious condition. She was nursed in a high concentration of oxygen, but her respiratory rate became irregular with intermittent periods of apnea and cyanosis. Her serum biochemistry showed evidence of a persistent acidosis which showed no response to intravenous injection of $\frac{1}{6}$ M lactate solution or sodium bicarbonate solution.

Death occurred at the age of 38 hours.

Biochemical estimations on donor blood for the third exchange

Plasma potassium = >20 mEq./L. (Colorimeter standardized to 20 mEq./L.)

CO_2 combining power = 7.7 mEq./L.

pH = 6.1

Biochemical estimations on infant's blood

Before third exchange transfusion
Potassium = 4.3 mEq./L.
At time of cardiac arrest
Potassium = 12.0 mEq./L.
At time of cardiac arrest
Calcium = 3.5 mEq./L.
At time of cardiac arrest
CO_2 combining power = 12.2 mEq./L.

Autopsy.—This was performed 12 hours after death. There was a slight icteric tinge to the skin as well as subconjunctival hemorrhages and petechiae over the trunk. Petechial hemorrhages were also seen subpleurally in the region of the trachea and lungs, in the heart, kidneys, and liver. The lungs were hemorrhagic in appearance in the lower portion and fleshy in consistence. Microscopic examination revealed areas of extramedullary hematopoiesis, which were marked in the liver but also present in the kidney. Hemorrhages were present within the lung, kidney, thymus, and adrenal. The lungs showed moderate atelectasis. Sections of the heart showed no remarkable histopathological change.

The causes of death were finally designated, according to their presumed degree of importance, as follows: (1) post-transfusion electrolyte imbalance; (2) hemolytic disease of the newborn; (3) prematurity; (4) hypoxia; and (5) pulmonary atelectasis.

Case 2.—*Cardiac Arrhythmia During Exchange Transfusion.*—

Experience with electrocardiography in 50 exchange transfusions performed on 36 infants has revealed one other example of gross cardiac arrhythmia. This infant weighed 2,160 Gm. and was of 35 weeks' gestation. The cord blood hemoglobin was 7.0 Gm. per cent and the bilirubin 6.82 mg. per cent. He received an exchange transfusion at the age of 1 hour, using 5-day-old partially packed blood. After injection of 185 c.c. of blood in 15 c.c. aliquots, the heart rate was suddenly slowed although the infant's general condition remained satisfactory. The ECG showed marked sinus bradycardia and occasional ectopic beats (Figs. 5 and 6). The arrhythmia was uninfluenced by injection of 1.5 c.c. calcium gluconate (10 per cent solution) and persisted until the end of a cautiously executed exchange of 450 c.c. of blood. The bradycardia alternated with periods of normal ECG configuration. ECG tracings taken on the first, second, third, and seventh days after the exchange transfusion were not remarkable and the infant's subsequent progress was uneventful.

Biochemical estimations on donor blood

Potassium = 9.7 mEq./L.
Calcium = 5.2 mEq./L.

Biochemical estimations on infant's blood

Before exchange transfusion
  Potassium = 6.9 mEq./L.
  Calcium = 5.0 mEq./L.
Mid-transfusion
  Potassium = 5.1 mEq./L.
  Calcium = 6.6 mEq./L.
Post-transfusion
  Potassium = 7.6 mEq./L.
  Calcium = 8.6 mEq./L.

The high figures for calcium in the mid- and post-transfusion samples could be due to contamination from immediately preceding injections of calcium gluconate solution.

DISCUSSION

Two examples of 2:1 auriculoventricular heart block detected by electrocardiographic examination during exchange transfusion have been reported by Joos, Yu, and Miller[3] (Table I). One infant, transfused with donor blood containing a plasma potassium of 8.0 mEq./L., developed parasystoles and 2:1 block intermittently during the fourth and fifth 100 c.c. of the exchange. The arrhythmia was uninfluenced by calcium administration and the infant's serum potassium did not rise above 5.40 mEq./L. The second infant, a premature weighing 1,190 Gm., was transfused with donor blood containing a plasma potassium of 18.6 mEq./L. Arrhythmia consisting of 2:1 heart block developed during administration of the second 50 c.c. of exchange, persisted for 4 minutes, and then reverted to normal rhythm following the intravenous injection of 0.1 Gm. of calcium gluconate. The serum potassium just before the onset of the 2:1 block was 9.12 mEq./L. This baby died within 24 hours of the exchange transfusion. Autopsy revealed the findings of prematurity, severe hemolytic disease of the newborn, and kernicterus. The heart was not abnormal.

Examples of cardiac arrest during exchange transfusion have been reported by Walker and Neligan (1 case).[4] Pew (1 case),[5] and Bolande, Traisman, and Philipsborn (4 cases).[6] These cases are summarized in Table I. Campbell[7] in a study of potassium levels in exchange transfusion has referred to 7 deaths in association with the transfusion. In 4 of these cases the infant's maximum potassium level ranged between 6.13 and 10.23 mEq./L.

manifested itself with clinical signs of pulmonary or cardiac distress, which have included rapid respiratory rate, cyanosis, pulmonary crepitations, gagging, and production of frothy mucus. In contrast to this, the clinical state of the infants, referred to in Table I, was such that no anxiety was felt regarding their condition until the sudden onset of the cardiac manifestations. It is most likely that these infants suffered from a complication of exchange transfusion other than that of congestive heart failure.

TABLE I. A COMPARISON OF BIRTH WEIGHT, VOLUME OF BLOOD TRANSFUSED, AND BLOOD CHEMISTRY IN REPORTED CASES SHOWING CARDIAC ARRHYTHMIA OR ARREST DURING EXCHANGE TRANSFUSION

AUTHOR	WT. OF BABY (GM.)	VOL. OF BLOOD INJECTED BEFORE CARDIAC ARREST OR ONSET OF ARRHYTHMIA (C.C.)	DONOR BLOOD POTASSIUM (MEQ./L.)	INFANT BLOOD AT TIME OF CARDIAC ARREST OR END OF EXCHANGE		CALCIUM GIVEN DURING EXCHANGE
				POTASSIUM (MEQ./L.)	CALCIUM (MEQ./L.)	
		With Electrocardiography				
Case 1	2,220	60	>20.0	12.0	3.5	Yes
Case 2	2,160	185	9.7	7.6	8.6	Yes
Joos, Yu, and Miller[3]	—	400	—	4.63	—	Yes
Joos, Yu, and Miller[3]	1,190	75	18.6	9.12	3.2	Yes
		Without Electrocardiography				
Walker and Neligan[4]	2,400	230	16.52	14.58	—	No
Pew[5]	—	350	—	4.5	2.85	Yes
Bolande et al.[6]	—	—	9.55	5.16	—	Yes
Bolande[6]	—	—	22.70	5.30	—	Yes
Bolande[6]	—	—	21.10	6.55	—	Yes
Bolande[6]	—	—	20.50	7.75	—	Yes

Table I shows an analysis of 10 infants who shared in common the electrocardiographic features of sudden onset of arrhythmia, 2:1 heart block, or the clinical features of sudden cardiac arrest. In so far as it can be ascertained from reading the reports of these cases, it seemed unlikely that any of them suffered from the type of congestive heart failure described by Walker and Neligan,[4] and Allen and Diamond.[1] Congestive heart failure in hemolytic disease of the newborn can be an insidious process but has usually

There was no definite evidence other than the clinical features and the electrocardiographic findings that the mechanism of the cardiac arrhythmia was the same in all 10 cases. Case 1 which showed a sudden progression from a state of slow nodal rhythm, without associated clinical features, to complete cardiac arrest in a period of 4 minutes suggested that there was a possible interrelationship in this group of cases. It seemed likely that in this case there was some biochemical derangement or other factor which, acting over a short period of time, severely embarrassed the heart action. Hyperpotassemia was not considered to be a likely cause. Serum potassium levels up to 7.8 mEq./L. have not been considered unusual (McCance and Young[8]) during the normal newborn period. Sudden cardiac arrest occurred with a potassium level as low as 4.5 mEq./L. in the infant reported by Pew.[5] In addition, Bolande[6] has reported 1 infant with a serum potassium of 17 mEq./L. who did not develop cardiac arrest during exchange and who survived the exchange transfusion for a period of 17 hours. A comparison of the potassium in the donor blood and the potassium in the infant's circulation in Table I suggested that most infants could handle comparatively large loads of infused potassium. This confirmed the observations of Campbell[7] and of Bolande.[6]

The possibility of cardiac arrest from hyperpotassemia also appeared unlikely from the experimental work of Baker and his co-workers.[9] They have reported the use of potassium citrate in the arrest of the perfused isolated hearts obtained from 4 stillborn fetuses of 16 to 20 weeks' gestation. A concentration of potassium citrate equivalent to 14.8 mEq./L. (calculated as tripotassium citrate) had to be directed as a continuous infusion into the coronary circulation to produce cardiac arrest. The volume of the potassium citrate solution required to produce this effect was not specified. Effler and his co-workers[10] have reported the use of potassium citrate solutions equivalent in strength to 230.0 mEq./L. (calculated as tripotassium citrate) and 6-20 c.c. volume to produce cardiac arrest in children undergoing cardiac surgery. In both reports the potassium solutions were directed into the coronary arteries and there was no opportunity for dilution to occur from mixture with venous blood. They have not, however, reported on the efficacy of weaker solutions of potassium. In exchange transfusion, the donor blood has ample opportunity to become diluted with the infant's venous blood before being directed to the coronary circulation.

Hypocalcemia was also considered as a cause of cardiac arrest. In 9 out of the 10 cases, calcium was given as a prophylactic measure during the exchange transfusion. In 2 cases of heart block and one of cardiac arrest, there was no response to immediate administration of calcium. It appeared unlikely, therefore, that calcium deficiency per se was the cause of the cardiac phenomena.

Pew[5] drew attention to the fact that his case of cardiac arrest followed shortly after the introduction of a bottle of cool blood into the exchange transfusion and that the heart felt cold when it was massaged. In Case 1 no attempt was made to warm the blood other than allowing it to stand at room temperature for about 10 to 15 minutes. Information with regard to warming of the blood is not available on the other cases. Hoff and Stansfield[11] and Deterling and his coworkers[12] have provided experimental evidence in the dog that ventricular fibrillation could develop when the body temperature was reduced below 73° F. or the local ventricular temperature below 50° F.

One factor which has not been given much consideration in previous reports is the effect that the acid-citrate dextrose anticoagulant mixture has on reducing the pH and CO_2 combining power of donor blood. On samples of donor blood tested at this hospital, the average pH was 6.2 and this level varied little with the duration of storage. In Case 1, severe and irreversible acidosis was an outstanding feature following the third replacement transfusion. Deterling[12] demonstrated that the ventricular fibrillation induced in dogs by hypothermia did not develop when the blood was maintained in a state of alkalosis by hyperventilation.

At the present time it is not possible to state that any one specific factor or combinations of factors is responsible for the occurrence of cardiac arrest in infants undergoing exchange transfusion. According to circumstances several or all of the following factors may be present: hyperpotassemia, hypocalcemia, cooling of the heart, acidosis, prematurity, and the disease process of hemolytic disease. There may be other factors at present unsuspected. The combined use of electrocardiography and adequate biochemical study is one way of further elucidating the problems involved and, at the same time, ensuring maximum safety for the infant.

SUMMARY

Attention is drawn to the fact that sudden and unexpected death may occur during or shortly after exchange transfusion for hemolytic disease of the newborn.

One case is reported of bradycardia, ventricular fibrillation, and cardiac arrest after 70 c.c. of blood had been exchanged. A second case is reported of bradycardia and arrhythmia developing after an exchange of 185 c.c. of blood.

These cases are compared with 8 other case reports in which there is a similarity of clinical or electrocardiographic findings. It is not possible from the data available to determine a common etiological factor for the sudden alteration in cardiac function.

It is suggested that possible factors which might be operating singly, or in combination, are hyperpotassemia, hypocalcemia, hypothermia, acidosis, prematurity, and the disease processes of hemolytic disease.

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STUDIES ON FETAL LIVER FUNCTIONS IN HOMO- AND HETEROSPECIFIC PREGNANCIES WITH SPECIAL REFERENCE TO THE ICTERUS PRAECOX OF THE NEWBORN

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CONTRARY to the great attention given during the last fifteen years to the pathogenetic role of the Rh factor in causing hemolytic disease of the newborn, relatively little attention has been paid to the A and B blood groups as a cause of this disease. This, despite the fact that not later than five years after the discovery of the ABO blood groups by Landsteiner, Dienst[1] first drew attention to the eventual damage that the ABO blood group incompatibility may cause to the mothers bearing children with blood groups incompatible with their own blood groups.

In 1923, Ottenberg[2] re-emphasized Dienst's conception, and two years later the definition of homo- and heterospecific pregnancies was coined by Hirszfeld and Zborovski, who again emphasized the damaging results of the antigen-antibody reaction in mothers and fetuses in heterospecific pregnancies.

The conception of these investigators has not been substantiated by subsequent investigations. It was not until 1945 that Polayes[3] first drew attention to the role of ABO blood group incompatibility in causing erythroblastosis fetalis in the newborn. Almost simultaneously we described (1944) the new clinical form of the hemolytic disease of the newborn, for which we proposed the name of "icterus praecox" and which has since been accepted by most authors.

In our previous communications,[4-6] we described in detail the clinical aspects of this mild variant of the hemolytic disease of the newborn which is mainly, but not exclusively, due to the ABO blood group incompatibility between mother and fetus.

During the past fifteen years we have been able to observe 190 cases of icterus praecox which appeared with a frequency of approximately 1 case in 120 to 130 deliveries.

Several conceptions have since been advanced by different authors to explain the striking difference in the gravity of the hemolytic disease of the newborn caused by the incompatibility of the Rh and ABO factors. These differences are the more surprising in that they are in contrast to expectations of what should really happen.

It is generally understood that the ABO and Rh systems are entirely independent of each other. It is furthermore evident that from the immunological point of view the former system is much more complete than the latter. Consequently we should expect to see more frequently severe reactions in

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ABO blood group incompatibilities than in cases of incompatibilities of the Rh factor. Not only has the ABO system naturally occurring antibodies which are lacking in the Rh system but, in addition, hemolysins and opsonins are always found in the blood of the mothers of newborn infants with hemolytic diseases caused by heterospecific pregnancies, whereas they are rarely, if at all, found in the maternal blood in Rh incompatibility.

The problem is further complicated by the presence of two variants of the A and B agglutinogens in the tissues and body fluids in secretors and of at least one, water-soluble variant in nonsecretors among the newborn infants, whereas the existence of a similar Rh substance in the tissues of the infants is denied by most investigators.[7-9]

In addition, changes in the osmotic fragility seem to be a characteristic feature of the fetal erythrocytes in heterospecific pregnancies, and microspherocytosis has been found exclusively in the syndrome of hemolytic diseases of the newborn caused by ABO blood group incompatibility.

In our first communication on icterus praecox we advanced the hypothesis explaining the mildness of the hemolytic disease of the newborn in heterospecific pregnancies by the presence of the A and B antigens in the tissues and body fluids of the newborn infant, especially in the secretor group, which neutralize the maternal alpha and beta immune antibodies circulating in the fetal blood. Plausible as this hypothesis seemed to us and to other authors, it has not been substantiated up to the present moment. Some investigators, on the other hand, have attributed damaging effects to the antigen-antibody reaction in the fetal tissues in cases of isoimmunization caused by heterospecific pregnancies.

The purpose of our present study was to investigate the liver functions of the newborns in homo- and heterospecific pregnancies with or without isoimmunization of the mothers by an ABO blood group incompatibility and to assess the degree of impairment of these functions resulting from an eventual antigen-antibody reaction in the fetal liver.

MATERIAL AND METHODS

Specimens of the cord blood of 120 newborn infants were examined and they were divided into the three following groups: *Group I*, 60 infants of homospecific pregnancies; *Group II*, 40 infants with blood groups incompatible with those of their mothers but without isoimmunization of the mothers against the ABO blood groups of the infants; *Group III*, 20 infants with icterus praecox due to the isoimmunization of the mothers against the ABO blood groups of their children.

A. *The total protein* concentration was determined in the serum of the cord blood by the biuretic method with the Kingsley modification for the separation of the albumin from the globulin, and an analysis of the different protein fractions was made by the paper electrophoretic method.

B. *The total bilirubin concentration* as well as the direct and indirect van den Bergh reaction was determined in the cord blood of all the newborn infants.

C and D. In addition, the *total cholesterol* and a battery of the following tests, generally considered as being related to the liver functions, have been determined in the cord blood serum: (1) The *Weltman coagulation band;* (2) the *cephalin-cholesterol flocculation test;* (3) the *thymol turbidity* and *flocculation tests;* and (4) the *Lugol test.*

RESULTS

A. *Proteins.*—

1. *Total proteins:* As shown in Table I, the mean value of the total protein concentration was found to be significantly lower in the blood sera of the newborn infants in heteropecific than in homospecific pregnancies and much lower in the blood of newborn infants with icterus praecox. These mean values were 5.99, 5 80, and 5.66 Gm. per cent in the three groups, respectively.

TABLE I. MEAN VALUES OF TOTAL PROTEIN, ALBUMIN, AND GLOBULIN CONCENTRATIONS IN THE CORD BLOOD IN HOMO- AND HETEROSPECIFIC PREGNANCIES WITH AND WITHOUT ISOIMMUNIZATION OF THE MOTHER

GROUP	TOTAL PROTEINS (GM. %)		ALBUMINS (GM. %)		GLOBULINS (GM. %)		ALBUMIN/ GLOBULIN RATIO
	AVERAGE	RANGES	AVERAGE	RANGES	AVERAGE	RANGES	
I. Homospecific pregnancies	5.99	(5.10-6.80)	3.97	(3.0-4.50)	2.02	(1.7-2.50)	1.97
II. Heterospecific pregnancies without isoimmunization	5.80	(5.1-6.7)	3.82	(3.1-4.4)	1.98	(1.4-2.6)	1.92
III. Heterospecific pregnancies with isoimmunization; icterus praecox	5.56	(4.9-6.6)	3.62	(3.1-4.3)	1.94	(1.6-2.5)	1.86

2. *Electrophoretic pattern:* The electrophoretic pattern of the cord blood serum proteins, on the other hand, showed no significant differences in the distribution of the protein fractions in the three different groups of newborn infants. The mean values of the protein fractions in the cord blood sera, expressed in percentage, were: 62.8, 3.8, 7.4, 8.4, and 17.5 Gm. per cent for the albumin, alpha 1, alpha 2, beta, and gamma globulin fractions, respectively. This electrophoretic pattern of the cord blood serum proteins is very similar to the proteinogram of the normal adult but contrasts somewhat with the electrophoretic pattern of pregnant women at term. This pattern of the maternal blood serum proteins is characterized by a relatively high concentration of the alpha 2, beta, and gamma globulins and by a low concentration of the albumin fraction. (Table II.) The increased concentration of the alpha 2 and beta globulins may be explained by the increase of cholesterol and lipoproteins in the blood of pregnant women contrasting with the low concentration of cholesterol, lipids, and lipoproteins characteristic in the fetal blood.

B. *Cholesterol* (Table III).—The mean values of the cholesterol concentration in the cord blood were 82.5, 73.5, and 85.5 mg. per cent for the three groups of newborn infants, respectively. The lower mean value of the cholesterol concentration in the

TABLE II. ELECTROPHORETIC PATTERNS OF THE SERUM PROTEINS IN THE CORD BLOOD AND IN THE VENOUS BLOOD OF THE MOTHERS (IN PERCENTAGE)

			GLOBULINS			
		ALBUMINS	ALPHA	ALPHA 2	BETA	GAMMA
Newborn infants	Average	62.8	3.8	7.4	8.4	17.5
	Ranges	52-73	1-6	5-11	6-13	10-21.5
Mothers	Average	46.7	5.5	12.2	13.8	21.8
	Ranges	39-55	5-8	10-15	12-18	15-29

TABLE III. MEAN VALUES OF TOTAL CHOLESTEROL, TOTAL BILIRUBIN, AND DIRECT VAN DEN BERGH REACTION IN CORD BLOOD IN HOMO- AND HETEROSPECIFIC PREGNANCIES

GROUP	TOTAL CHOLESTEROL (MG. PER CENT)	TOTAL BILIRUBIN (MG. PER CENT)	DIRECT VAN DEN BERGH REACTION (PERCENTAGE)
I. Homospecific pregnancies			
Average	82.5	1.23	60
Ranges	65-128	0.3-3.8	
II. Heterospecific pregnancies			
Average	73.5	1.25	61
Ranges	60-105	0.3-2.1	
III. Icterus praecox			
Average	85.5	3.35	80
Ranges	55-113	0.9-7.5	

cord blood in heterospecific pregnancies (see Group II) does not seem to be significant enough and is, furthermore, in contrast with the mean value of the third group of newborn infants (heterospecific pregnancies with isoimmunization of the mothers) which was similar to the mean value of the first group, to permit us to draw any conclusion.

C. *Bilirubin.*—

1. *Total bilirubin*: The total bilirubin concentration was increased in the cord blood of almost all the newborn infants in comparison with normal values in healthy adults. The mean values of the bilirubin concentration were 1.23, 1.25, and 3.35 mg. per cent in the cord blood of the three groups of newborn infants, respectively. No difference in the bilirubin concentrations was therefore found between the homospecific and the heterospecific group without isoimmunization of the mother. The group of icterus praecox due to isoimmunization of the mother, on the other hand, was characterized by a very high bilirubin concentration in the cord blood. On the average, this concentration was almost three times as high as the mean value in the two other groups. The bilirubin concentration in the cord blood can therefore serve to predict, or at least to raise suspicion of, the appearance of icterus praecox in the newborn.

2. The *direct van den Bergh reaction*: This reaction was positive in 60, 61, and 80 per cent of the cord blood sera in the three groups, respectively, the mean values of the direct bilirubin concentration being 0.52, 0.46, and 0.92 mg. per cent for the three respective groups.

D. *Coagulation, Turbidity, and Flocculation Tests* (Table IV).—

1. The *Weltman coagulation* band showed a slight shift to the right in the blood of all the newborn infants, covering 7 to 8 tubes irrespective of

TABLE IV. COAGULATION FLOCCULATION AND TURBIDITY TESTS IN CORD BLOOD IN HOMO- AND HETEROSPECIFIC PREGNANCIES

GROUP	WELTMAN COAGULATION BAND (NUMBER OF TUBES)	CEPHALIN TEST POSITIVE REACTIONS (PER CENT)	THYMOL TURBIDITY (UNITS)	LUGOL TEST
I	7-8	50	0.73	Neg.
II	7-8	65	0.64	Neg.
III	7-8	76	1.50	Neg.

the group to which they belonged, with the exception of two cases of icterus praecox in which the coagulation band showed an extreme shift to the left covering no more than 1 to 2 tubes.

2. The *cephalin-cholesterol flocculation test* gave positive results in 50 per cent of the cord bloods of the homospecific group of pregnancies, in 65 per cent in the heterospecific group without isoimmunization of the mothers, and in 80 per cent of the group of newborn infants with icterus praecox.

3. The *thymol turbidity test* showed remarkably low values in the cord blood of all the newborn infants, but the mean value was definitely higher in the cord blood of those with icterus praecox. The mean values were 0.75, 0.65, and 1.50 units for the three groups, respectively.

The *thymol flocculation test* was negative in the cord blood of all the newborn infants.

4. The *Lugol test* was negative in the blood sera of all the newborn infants with very few exceptions, irrespective of the group to which they belonged.

DISCUSSION

None of the explanations so far given by different authors to elucidate the mildness of the hemolytic disease of the newborn caused by the ABO blood group incompatibility, contrasting with the severity of the same disease due to the Rh incompatibility, has proved to be satisfactory.

Neutralization of the maternal alpha and beta immune antibodies circulating in the fetal blood after having passed through the placental barrier, by the A and B antigens of the tissues and body fluids of the fetus, is still the most plausible conception hitherto brought forward.

Yannet and Lieberman[10] indeed found a significantly greater incidence of ABO blood group incompatibilities between children with mental deficiencies which could not be explained as postinfectious or posttraumatic, and their mothers, than between normal mothers and children. According to these authors, the mental deficiencies of these children may, partly at least, be explained by damage in the brain tissues caused by an antigen-antibody reaction.

Johnstone[11] found higher values of bilirubin concentration in the cord blood of heterospecific than in those of homospecific pregnancies. He too believes that an antigen-antibody reaction in the liver cells is the cause of the raised bilirubin concentration in the cord blood of heterospecific pregnancies.

The meaning of these observations seems to us to be that even the naturally occurring alpha and beta antibodies may have cytotoxic qualities, and it may be assumed that the immune antibodies of the ABO system possess these qualities to a much greater degree. Consequently, the passage of these antibodies from the maternal to the fetal blood and their junction with the A and B antigens in the fetal tissues may have injurious effects on the respective organs.

Our findings corroborate to a certain degree the above-mentioned observations.

We did not find a more pronounced total bilirubin concentration in the cord blood in heterospecific pregnancies without isoimmunization of the mothers, than in the homospecific group. The percentage of the direct van den Bergh reaction was likewise identical in both groups of newborn infants. On the other hand, we found lower total protein concentrations and a higher percentage of positive cephalin reactions in the hetero- than in the homospecific group.

An eventual moderate degree of damage of the fetal liver tissues superimposed on the "physiological" immaturity of the fetal liver therefore cannot be excluded entirely in heterospecific pregnancies in general and in cases of isoimmunization of the mothers in particular.

The impairment of the fetal liver functions was especially evident in the newborn infants with icterus praecox. In the cord blood of these infants we found particularly low total protein concentrations, high bilirubin values, a very high percentage of positive van den Bergh reactions, and a much higher percentage of positive cephalin flocculation tests than in the cord blood of the other groups of newborn infants. In addition, we found, in two cases of icterus praecox, a shift to the extreme left of the Weltman coagluation band which is certainly not without significance.

At the present stage of our investigations no more can be said than that the impaired liver functions of the newborn infant probably play a much greater role in the pathogenesis of the hemolytic disease of the newborn than hitherto admitted. Whether the conspicuous impairment of the fetal liver functions in heterospecific pregnancies is the direct result of an antigen-antibody reaction in the fetal liver remains to be elucidated by further investigations.

SUMMARY

The liver functions of 120 newborn infants were determined by examination of the blood chemistry of their cord blood.

The influence of the heterospecific pregnancies on the liver functions of the infants was examined by comparing the blood chemistry of the cord blood in homo- and heterospecific pregnancies.

The mean values of the total protein concentrations were found to be lower in the cord bloods of the hetero- than in those of the homospecific group. It was especially low in cases of icterus praecox due to isoimmunization of the mother.

A high total bilirubin concentration and a high percentage of direct bilirubin reactions (80 per cent) were found in the cord blood of newborn infants with icterus praecox, but no difference between the degree of the "physiological" hyperbilirubinemia of the cord blood of homo- and heterospecific pregnancies could be found.

The cephalin flocculation test gave more frequently positive results in hetero- than in homospecific pregnancies.

The thymol turbidity test showed higher values in the blood of newborn infants with icterus praecox.

It is suggested that the ABO blood group incompatibility between mothers and children may be considered as being responsible for the impairment of the liver functions of the newborn in heterospecific pregnancies and especially in cases of isoimmunization of the mother.

Editorial Note: Recent evidence has demonstrated that the excretion of water-insoluble indirect bilirubin involves its conversion to a direct-reacting water-soluble pigment by conjugation with glucuronic acid. The formation of bilirubin glucuronide in the liver depends upon the transfer by an enzyme glucuronyl transferase. According to this concept, the newborn with physiologic jaundice is handicapped by a delay in the formation of bilirubin glucuronyl transferase at birth. The effect of this delay is most pronounced in erythroblastosis where red-cell breakdown is excessive, as a result of which the newborn infant is exposed to high plasma concentrations of indirect bilirubin.*

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PSEUDOMONAS AERUGINOSA INFECTIONS: REPORT OF TWO PATIENTS WITH MENINGITIS

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IT IS quite generally believed that pseudomonas infections (*Bacillus pyocaneus*) are more frequent and of greater severity now than some years ago. The change that has taken place is attributed to a modification of the bacterial flora in the body brought about by the extensive use of the antibiotics.[1, 2]

Pseudomonas aeruginosa infections have been assigned to various sources which include head injuries, extension from focus in ear or sinus, genito-urinary conditions, operations for spinal cord tumor or laminectomy; also spinal anesthesia and intrathecal therapy. In 1947, Stanley[3] reported that, up to that time, 41 cases of primary *B. pyocyaneus* meningitis had been published; of that number, 32 (78 per cent) were the direct result of lumbar puncture. Infections of the umbilicus in the newborn have been recorded, possibly due to the organism being air-borne in the ward. A contaminated milk[4] supply has been incriminated also as being responsible for an epidemic in a newborn nursery where in 24 infants there were 9 deaths.

Skin lesions are common but none may occur. There may be only diarrhea,[4] which is bloody, and dehydration. But cutaneous lesions and hemorrhagic conditions are usually described in the severe cases[1, 3] and, in these, septicemia with positive blood cultures may be expected.

Because the vascular[5] system is likely to be attacked, numerous and often fatal complications follow. Necrosis may occur in any location of the entire gastrointestinal tract. Ecthyma gangraenosum may be a terminal complication.

Clement and Millard[1] state that meningitis is the commonest internal complication, the focus being otitis media, mastoiditis, or sinus infections. However, meningitis as a complication of *Ps. aeruginosa infection* is rarely reported in infants and it is extremely infrequent in adults. It is because of the latter situations that we believe our 2 patients are of unusual interest.

Abdominal distention[5] has been regarded as a characteristic finding in *Ps. aeruginosa* septicemia. Nevertheless, it was not evident in Case I. In the other instance (Case II), the patient's abdomen was tense but actual distention was not notable.

In both of our patients, petechiae were present in the skin. The child had more on the feet and ankles than in any other locality, but the man had petechiae more widely and evenly distributed over the entire surface of the body.

From Cook County Contagious Disease Hospital and Chicago Medical School.

Cutler and Cutler[6] have directed attention to a simple means of establishing a bacteriologic diagnosis in cases of *Pseudomonas meningitis* without awaiting a culture report. The procedure consists of exposing the spinal fluid to ultraviolet light. By doing so, "the spinal fluid even though colorless will show a greenish fluorescence." By resorting to this prompt method for identifying the organism, appropriate therapy can be instituted immediately.

It may be noted in the case histories that the child (Case I) was treated throughout with oxytetracycline although found to be more sensitive to streptomycin. The man (Case II) did not respond well to oxytetracycline; nor was polymyxin B effective. It was then disclosed by the laboratory that the infecting organism was more sensitive to Chloromycetin than to polymyxin B,[7] although the latter is often regarded as the drug of choice for combating *B. pyocyaneus* infections. But some investigators[1, 4] have found that almost immediate improvement may be gained by injections of 1.0 per cent methylene blue.

CASE REPORTS

CASE I.—On July 31, 1957, a 15-month-old Negro boy was hospitalized at Cook County Contagious Disease Hospital. He was said to be in good health until he developed fever one day prior to admission. A local physician saw him and prescribed pink tablets (sulfathiazole?). The mother stated she was directed to administer one tablet every 4 hours and did so on 3 occasions. Despite the medication, temperature elevation persisted and slight swelling of the face appeared. The following morning, the patient had two soft stools and one episode of emesis. The child was brought to the hospital in the early afternoon.

On admission, the temperature was 101° F., pulse was 120, respirations were 30, and blood pressure was 96/50 mm. Hg. The patient was a well-developed, well-nourished, male infant appearing acutely ill and slightly listless. The head was normal. There was slight puffiness about both eyes. Conjunctivae showed a few areas of punctate hemorrhage. Pupils and fundi were negative, bilaterally. Eardrums were seen with minimal injection but without drainage. A questionable nuchal stiffness was present. The heart and lungs were negative. Abdominal examination was unrevealing. There were scattered petechiae over the extremities, particularly prominent on both feet which were slightly edematous; there was, also, pretibial edema. Reflexes were normal. No Kernig or Brudzinski sign was detected.

Lumbar puncture was performed in view of possible meningococcemia with meningitis. Slightly turbid fluid was obtained. The cell count was 1,334 per millimeter, lymphocytes 1,243, polymorphonuclears 91. No organisms were seen on gram-stained smear. Additional laboratory data included hemoglobulin, 47 per cent; red blood count, 3,400,400; white blood count, 15,200 with differential neutrophils 64 per cent, band 15 per cent, lymphocytes 15 per cent, and monocytes 5 per cent. Cerebrospinal fluid showed glucose 57, protein 22, and chloride 107 milligram per cent. The Pandy reaction was positive. Later culture of spinal fluid specimen grew out *Pseudomonas aeruginosa* in two tubes, in one of which there was also *Escherichia coli*. Blood culture revealed enterococci. Urinalysis done repeatedly was negative for albumin, sugar, acetone and was negative, also, on microscopic examination. Blood serology for syphilis was negative. Bacterial sensitivity studies of antibiotics showed Pseudomonas and Escherichia to be sensitive to streptomycin, less so to tetracycline (10 to 50 mcg.) and resistant to chloramphenicol (more than 50 mcg.). Enterococci had susceptibility to erythromycin, tetracycline, chloramphenicol, and slight sensitivity to penicillin.

For approximately the first forty-eight hours, tetracycline, 75 mg. per kilogram of body weight, four times daily, was administered intravenously. This was followed by oral medication of similar dosage (125 mg.) every four hours. The clinical response to the regime was remarkable. The patient became completely afebrile on the fourth hospital day and remained essentially so thereafter. Slight puffiness on the face was observed as late as the sixth hospital day but subsided completely soon afterward. Otherwise, the patient was perfectly asymptomatic except for the existence of healing petechiae and few confluent necrotic lesions which were still evident over the extremities and hips during the last week of his hospital stay. The parents took the patient out of hospital against medical advice on Aug. 12, 1957, which was the fourteenth day after the onset of his illness. The child was symptom free at that time, after 12 days' treatment. In accord with a long-established custom in this hospital, there was no intrathecal therapy nor were lumbar punctures made for drainage.

Case II.—*History.*—A 29-year-old white man was admitted to a medical ward of Cook County Hospital on Oct. 14, 1953. He was disoriented so that a completely coherent statement was not obtainable. However, the patient was able to relate that he had a sore throat, had been coughing for a week, and that during the past two days had experienced severe headaches and repeated attacks of vomiting. It was also ascertained that he had been drinking to excess during the past eleven years and he claimed to have had a similar illness in 1943 after drinking "White Lightning."

Physical examination revealed a well-developed white man of fair nourishment who was confused and somnolent. There was a diffuse macular rash, pink in color, which involved the surfaces of the entire trunk and extremities. The pulse was 94, temperature was 101° F., rectally, and blood pressure was 110/84 mm. Hg. The pupils were equal and reacted to light and accommodation. The conjunctivae were moderately injected. The fundi could not be visualized adequately. Nucal rigidity was marked. The heart and lungs presented no unusual findings. Abdominal examination was negative except for slight tenseness and hyperactive bowel sounds. Genitalia and rectal examinations disclosed no abnormalities. Brudzinski, Gordon, and Oppenheimer signs were positive on the left. On the same side, the patellar reflex was increased and ankle clonus elicited. There was weakness and carpopedal spasm of the left hand.

A lumbar puncture was performed and recorded an opening pressure of 300 ml. of water. Approximately 12 c.c. of purulent fluid was released. The closing pressure was 120 ml. of water. The cell count was 8,000 polymorphonuclears but a gram stain disclosed no organisms. The Pandy reaction was positive. The patient was then transferred to the Contagious Disease Department (Cook County Contagious Disease Hospital) where he was given tetracyline (Terramycin) immediately, 250 mg. intravenously, and supportive treatment. The same dosage and route for Terramycin therapy was continued every four hours for eight days.

Hospital Course.—On the second hospital day, the rash had entirely disappeared and the patient was much more rational. The laboratory report of chemistry for spinal fluid stated glucose was 75 mg. per cent and protein was 550 mg. per cent. Blood chemistry for chlorides sodium, total protein, and NPN were within normal limits. Serum K was 7.1. Blood serology and agglutination tests for typhoid, Brucella, and Salmonella were all negative. Due to an unforseen delay, the result of culture of the spinal fluid was not received until the eighth hospital day. Both *Pseudomonas aeruginosa* and *Aerobacter aerogenes* were reported. The blood culture was positive for nonhemolytic streptococci. Although the patient had shown marked improvement clinically during eight days of Terramycin therapy, he continued to have a septic temperature. Treatment was then changed to streptomycin for two days without alteration of the fever pattern which ranged from normal to 103.8° F. orally. At this time a complete blood count was made; hemoglobin 95 per cent, leukocytes 14,500, with a shift to the left. Red blood count was 4,200,000.

An eye consultation did not reveal any signs of increased intracranial pressure. A spinal tap was made and 1,600 polymorphonuclear cells reported in the spinal fluid with glucose 35 mg. per cent and protein 130 mg. per cent. No organisms were seen on smear and culture was negative.

On the tenth hospital day, polymyxin B, 150 mg., daily in three divided doses intramuscularly, was substituted for streptomycin but septic temperature persisted. Urinalysis was performed daily including culture and blood NPN every other day. In the meantime, sensitivity tests had shown that *Pseudomonas aeruginosa* and *Aerobacter aerogenes* were more sensitive to chloromycetin than to Terramycin or to Aureomycin. After five days of polymyxin B therapy without change in the fever curve, Chloromycetin was substituted as a remedy and administered orally, 250 mg. every six hours. Within twenty-four hours following the institution of this therapy the temperature receded to normal and remained so. Four days later (the nineteenth hospital day) all medication was discontinued. A final lumbar puncture was performed on the twenty-first hospital day and the spinal fluid was found to be normal in all respects except for a slight elevation of protein. The patient was discharged completely asymptomatic on the twenty-third hospital day.

COMMENT

We wish to emphasize that neither of the 2 patients received any intrathecal therapy; nor were spinal taps performed for drainage[8] to "relieve intracranial pressure." However, for any form of meningitis, sensitivity tests should be made for several of the remedial agents in order to determine whether the drug being employed is the most effective. Both patients recovered without complications and their treatment was not beset with unnecessary procedures which sometimes prove to be harmful.[9] Fatality rates for groups of patients with *Ps. aeruginosa* meningitis have ranged from 55 per cent to approximately 90 per cent.

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diagnosis can be made solely on clinical grounds because the picture is quite distinctive, although the manifestations show variation in all three main symptoms.

It is assumed that a single recessive gene mutation is responsible for this syndrome. Exogenous factors like premature birth, difficult delivery, and infections in infancy apparently have no significance in the causation of this syndrome.

There is no recognized treatment for this condition. As far as the prognosis is concerned, Sjogren and Larsson reported that all their patients were totally incapacitated and none of them married and none had children. The mean expectation of life for those affected did not exceed half that of the general population.

SUMMARY AND CONCLUSIONS

A case of mental deficiency, spasticity, and congenital ichthyosis in a 7-year-old white male of German and Italian extraction is reported and a review of the available Scandinavian literature is presented.

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I have just seen the operation of transfusion, in a case of malignant cholera, performed by Dr. F. T. Ferris. The subject was Mrs. Rice, No. 105 Broome street, about 50 years of age.

Before the operation was performed, this female appeared to be in the last stage of disease; she had lost the power of speech; she had no pulse; her extremities and tongue were cold; her hands and feet blue, and her whole appearance indicated immediate dissolution.—Dr. Ferris was in attendance, and as the last resort performed the operation of transfusing into the veins a quantity of warm water, impregnated with muriate and sub carbonate of soda. The breathing became natural, the pulse gradually appeared at the wrist, the heat of the surface was restored, the natural color of the skin re-appeared, her voice became natural, and in fact she was *literally restored from death to life.* Her eyes, from being glassy and death-like, became natural and sprightly; her voice was strong, and she actually began to direct some of the domestic concerns of her family. I left her about two hours after the operation had been commenced, expressing her gratitude to the doctor, for his exertions, and thanking her God for her comparative restoration.

I send you this hasty account of the operation for publication, hoping the doctor himself will soon give a more minute detail of the case.

H. M. D.

FROM THE AMERICAN MERCURY (Hartford, Connecticut) July 30, 1832. (Apparently copied from some New York newspaper.)

A RELIABLE PAPER-STRIP METHOD FOR THE DETECTION OF PHENYLKETONURIA

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UNTIL 3 years ago, prompt recognition of phenylketonuria was relatively unimportant. However, recent reports indicate that effective dietary management, started early in life, can prevent the severe mental retardation usually associated with this condition.[1, 2, 3] The incidence of phenylketonuria is so low (1 in 20,000 live births) that a quick but reliable screening test is essential if the diagnosis is to be made frequently before evidence of retardation develops.

A screening test for the detection of phenylketonuria should require a small amount of urine, be relatively independent of cumbersome collection, and have a readily apparent color change when 30 mg. per cent or more of phenylpyruvic acid is present in the urine. A reliable paper-strip method would have the additional advantages of speed and convenience. In our hands, a technique which utilizes a chemically treated paper stick fulfills these criteria satisfactorily.

METHODS

Suitable test material was prepared by impregnating a portion of a paper stick (1/4 by 2 in.) with ferric chloride and glacial acetic acid and allowing it to dry.* A positive reaction was said to have occurred if the chemically treated portion of the paper turned green, gray, or dark blue within 60 seconds of its immersion in the solution submitted for examination. In serial dilution tests, four or more observers interpreted the reactions independently. Two individuals had had no previous experience with either the paper or the tube method. The latter test is performed by observing the color formed following the addition of 5 per cent ferric chloride to a solution acidified by glacial acetic acid. A blue-green or black color indicates the presence of phenylpyruvic acid; a brown or white color bears no relationship to its presence.

The paper strips were tested in four ways.

A. Solutions containing known but varying amounts of phenylpyruvic acid in distilled water were tested separately by the paper and the tube methods.

B. A stock solution of 100 mg. per cent of phenylpyruvic acid in distilled water was diluted with urine of non-phenylketonuric children. Solutions containing known but varying amounts of phenylpyruvic acid in urine from

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*After initial tests had indicated their practicability, these sticks were supplied in an improved form by Ames Laboratories, Elkhart, Ind.

6 nonphenylketonuric children were tested by each method.

C. Specimens of urine from patients known to have phenylketonuria were tested by each method. Some of these specimens had been voided 5 to 10 minutes previously; others had been frozen and stored for periods up to 16 months. All specimens were allowed to stand at room temperature and were tested periodically until both the paper and the tube tests became negative.

D. The results of periodic tests with the paper strips were recorded on one phenylketonuric child after her usual diet had been replaced by one containing not more than 15 mg. per kilogram of body weight of phenylalanine per day. Determinations of the phenylalanine levels in the serum and in the 24-hour urine specimens were made periodically until the paper and tube tests for phenylpyruvic acid became negative.

RESULTS

A. A light green color appeared on the test strip after it had been dipped in solutions containing 5 to 10 mg. per cent of phenylpyruvic acid in distilled water. This color change was readily apparent to inexperienced observers in solutions containing 10 mg. per cent. By the test tube method, inexperienced observers recorded positive readings in solutions containing up to 20 mg. per cent. With practice, a color change could usually be detected by the tube method in solutions containing 10 to 15 mg. per cent.

B. Definite color changes were apparent by the paper method in solutions containing urine with known amounts of 30 mg. per cent or more of phenylpyruvic acid. In some instances, 20 mg. per cent could be easily detected by inexperienced observers. Clearly definite color changes were apparent by the tube method in solutions containing from 20 mg. per cent to 40 mg. per cent, depending upon the experience and skill of the investigator. In solutions with concentrates of phenylpyruvic acid of 15 to 30 mg. per cent, the color changes on the paper strip were easier to interpret in each instance than were those in the test tube.

C. Twenty-five specimens of urine from phenylketonuric patients were positive initially by both methods. These specimens were tested repeatedly for 6 to 72 hours until the paper test was only faintly positive. At this time, the tube method was frequently indeterminate. In every instance, the color change was apparent for a longer time on the paper than in the tube.

D. *Low Phenylalanine Diet.*—During an observation period of one week prior to the institution of a low phenylalanine diet for an affected child, determination of the phenylalanine level in four 24-hour urine specimens varied from 30 to 40 mg. per cent. Four determinations of the concentration of phenylalanine in the serum varied from 40 to 50 mg. per cent. Two days after the diet had been instituted, the level of phenylalanine in the serum was 35 mg. per cent, and in the 24-hour urine, 40 mg. per cent. The test strips were positive until the sixth day. The concentration of phenylalanine in the serum was 15 mg. per cent both before and after the collection of a 24-hour urine on the sixth day. This specimen of urine contained less than 5 mg. per cent of phenylalanine.